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Randomized Phase IIb Study of Brimonidine Drug Delivery System Generation 2 for Geographic Atrophy in Age-Related Macular Degeneration

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Purpose: To evaluate the safety and efficacy of repeat injections of Brimonidine Drug Delivery System (Brimo DDS) Generation 2 (Gen 2) containing 400-μg brimonidine in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Design: A phase IIb, randomized, multicenter, double-masked, sham-controlled, 30-month study (BEACON).

Participants: Patients diagnosed with GA secondary to AMD and multifocal lesions with total area of > 1.25 mm^2 and ≤ 18 mm^2 in the study eye.

Methods: Enrolled patients were randomized to treatment with intravitreal injections of 400-μg Brimo DDS (n = 154) or sham procedure (n = 156) in the study eye every 3 months from day 1 to month 21.

Main Outcome Measures: The primary efficacy endpoint was GA lesion area change from baseline in the study eye, assessed with fundus autofluorescence imaging, at month 24.

Results: The study was terminated early, at the time of the planned interim analysis, because of a slow GA progression rate (~ 1.6 mm^2/year) in the enrolled population. Least squares mean (standard error) GA area change from baseline at month 24 (primary endpoint) was 3.24 (0.13) mm^2 with Brimo DDS (n = 84) versus 3.48 (0.13) mm^2 with sham (n = 91), a reduction of 0.25 mm^2 (7%) with Brimo DDS compared with sham ($P = 0.150$). At month 30, GA area change from baseline was 4.09 (0.15) mm^2 with Brimo DDS (n = 49) versus 4.52 (0.15) mm^2 with sham (n = 46), a reduction of 0.43 mm^2 (10%) with Brimo DDS compared with sham ($P = 0.033$). Exploratory analysis showed numerically smaller loss over time in retinal sensitivity assessed with scotopic microperimetry with Brimo DDS than with sham ($P = 0.053$ at month 24). Treatment-related adverse events were usually related to the injection procedure. No implant accumulation was observed.

Conclusions: Multiple intravitreal administrations of Brimo DDS (Gen 2) were well tolerated. The primary efficacy endpoint at 24 months was not met, but there was a numeric trend for reduction in GA progression at 24 months compared with sham treatment. The study was terminated early because of the lower-than-expected GA progression rate in the sham/control group.

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Supplemental material available at www.ophthalmologyretina.org.

Age-related macular degeneration (AMD) is the primary cause of irreversible legal blindness and visual disability for adults aged ≥ 50 years in the developed world.[1] Geographic atrophy (GA), an advanced form of AMD, is present in ≥ 1 eye in the majority of patients with advanced AMD[2] and accounts for approximately 25% of the severe visual impairment attributed to AMD.[3] The global prevalence of GA is estimated at approximately 5 million, representing 0.44% of the adult population.[4]

Geographic atrophy is a progressive disease, and there are no approved treatments. A progressive loss of the retinal pigment epithelium (RPE), photoreceptors, and the choriocapillaris layer leads to severe, irreversible vision loss in the advanced state of the disease. One potential goal of

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treatment is to slow the progression of the disease, thereby delaying the progressive loss of vision and maintaining the quality of life by avoiding the potential negative impacts of vision loss, such as decreased ability to drive or read, loss of independence, and increased risk of falls and fractures. Another potential goal of treatment is to restore function using a stem cell–based therapy or other regenerative medicine approach.[5–8]

Brimonidine is a highly selective α2-adrenergic receptor agonist with a long history of ophthalmic use for reducing intraocular pressure in patients with open-angle glaucoma or ocular hypertension.[9] In addition, brimonidine has cyto/neuroprotective effects that may result in the RPE and photoreceptors becoming resistant to injury. Cyto- and neuroprotective effects of brimonidine in the retina have been demonstrated in cultured cells in vitro,[10] in animal studies,[11,12] and in humans with normal-tension glaucoma treated with topical brimonidine.[13] In vitro, brimonidine preserves mitochondrial membrane potential, reduces production of toxic reactive oxygen species, and preserves cell viability in human RPE (ARPE-19) and Müller (MIO-M1) cells exposed to hydroquinone.[10] The α2-adrenergic receptor is expressed by both RPE and neuronal cells (e.g., photoreceptors and retinal ganglion cells), and its activation by brimonidine has cascading effects on signaling pathways that block apoptosis.[11] Activation of the α2-adrenergic receptor upregulates expression of growth factors, such as basic fibroblast growth factor, suppresses accumulation of excitotoxic levels of glutamate that cause neuronal cell death, and alters synaptic transmission via modulation of N-methyl-D-aspartate receptors, reducing hyperpolarization and calcium entry.[11,14,15] It is postulated that brimonidine protects RPE cells and photoreceptors, making them more resistant to injury and therefore preserves their function via a combination of these mechanisms. However, the administration of brimonidine via eye drops does not deliver adequate concentrations of brimonidine to the outer retina for neuro/cytoprotective effects.

An intravitreal implant containing brimonidine in a biodegradable poly-(D,L-lactide) polymer matrix, Brimonidine Drug Delivery System (Brimo DDS; Allergan, an AbbVie company) has been developed for the potential treatment of GA. The implant is administered using a proprietary applicator system and provides slow release of brimonidine into the vitreous humor for several months, as the polymer matrix degrades. The first generation of the implant, containing a dose of 132- or 264-μg brimonidine (formulated as 200- or 400-μg brimonidine tartrate), was evaluated in a phase IIa, randomized, multicenter, double-masked, sham-controlled, 24-month study (NCT00658619) in patients with GA secondary to AMD.[16] The study enrolled 119 patients aged ≥ 50 years with bilateral GA attributed to AMD, with GA area between 0.75 and 12 disc areas (2.02–32.28 mm^2) in both eyes. Best-corrected visual acuity (BCVA) letter score at screening, measured using the ETDRS method, was between 70 and 35 letters (20/40 and 20/200 Snellen equivalent) in the study eye and at least 25 letters (20/320 Snellen equivalent) in the fellow eye. Patients were randomized 2:2:1 to Brimo DDS Generation 1 (Gen 1) 132 μg, Brimo DDS Gen 1 264 μg, or sham procedure administered at baseline and month 6. The mean GA area growth was consistently but not statistically significantly reduced in the Brimo DDS Gen 1–treated groups. At the 12-month primary timepoint, the mean GA area growth was reduced by 19% and 28% relative to sham treatment in the 132- and 264-μg Brimo DDS Gen 1 groups, respectively.[16] In patients with a baseline GA lesion area of ≥ 6 mm^2 (two-thirds of all patients), the effects of both 132-μg and 264-μg Brimo DDS Gen 1 in reducing the mean GA area growth were statistically significant.[16] The safety profile was favorable.[16]

Following the phase IIa study, the product was reformulated to Generation 2 (Gen 2) to achieve faster drug release and higher retinal brimonidine concentrations. In the Gen 2 reformulation, brimonidine tartrate was replaced by brimonidine free base, resulting in an approximately 50% higher active drug load compared with the Gen 1 264-μg implant. The implant polymer was also changed to a poly (D, L-lactic-co-glycolic acid)/(D, L-lactic acid) blend that biodegrades faster, resulting in more rapid release of brimonidine and higher retinal levels. Studies in monkeys showed that at 3 months after administration, drug release from 400-μg Brimo DDS Gen 2 was complete, and macular brimonidine concentrations were at least threefold higher than the minimal effective concentration in models of retinal degeneration (AbbVie data on file). Pharmacokinetic/pharmacodynamic modeling (AbbVie data on file) further suggested that dosing every 3 months would maintain brimonidine concentrations in the retina equivalent to the concentrations that protected photoreceptors in acute photo-oxidative models of retinal degeneration.[17] The Gen 2 reformulation also included a modification in the size of the implant (the diameter was reduced) to permit its delivery with a smaller 25-gauge needle rather than the 22-gauge needle used with the previous formulation, for greater patient comfort and fewer injection-related adverse effects.

The objective of this phase IIb study was to evaluate the safety and efficacy of repeat injections of Brimo DDS Gen 2 containing 400-μg brimonidine on retinal structure and visual function in patients with GA secondary to AMD. Injections were performed every 3 months through month 21. The clinical hypotheses were as follows: (1) Brimo DDS (Gen 2) is safe and well tolerated with repeated administration, and (2) Brimo DDS (Gen 2) is more effective than sham treatment in slowing the growth of GA lesion area and the loss of standard and low-luminance BCVA in patients with GA secondary to AMD.

Methods

This phase IIb, multicenter, double-masked, randomized, sham-controlled, 30-month study (BEACON) was designed to evaluate the safety and efficacy of Brimo DDS Gen 2 in patients with GA secondary to AMD. The study adhered to the tenets of the Declaration of Helsinki and was conducted in compliance with the International Conference on Harmonization E6 guideline for Good Clinical Practice. An institutional review board or independent ethics committee (Administrative Secretariat Independent Ethics

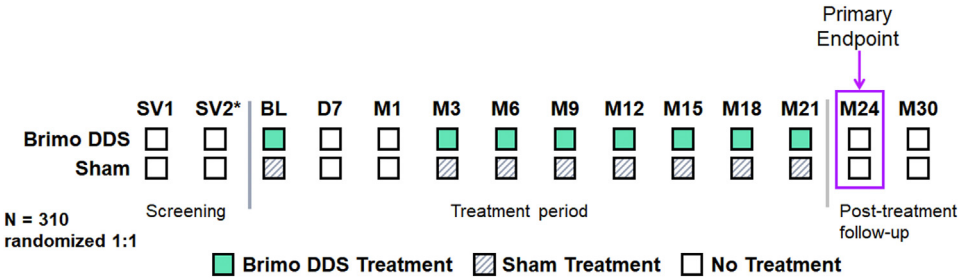

Figure 1. Study schematic. *A second screening visit was required only for patients participating in the microperimetry procedure, which was performed at selected sites. BL = baseline (day 1), Brimo DDS = 400-μg Brimonidine Drug Delivery System Generation 2; SV = screening visit.

Committee A.O.U. of Cagliari, Bellberry HREC, Chesapeake Research Review (Advarra), CESC of the Province of Padua, Ethics Committee of the IRCCS San Raffaele Hospital in Milan, Ethics Committee of Milan Area A, Ethics Committee of Milan Area B, Ethics Committee of the University Hospital of Bologna, Ethics Committee of the University Hospital of Tübingen, Ethics Committee of the University of Bonn, Hôpital Ambroise Paré Laboratoire d'Anatomopathologie, Intercompany Ethics Committee Molinette Hospital, NRES Committee London, Oregon Health and Science IRB, Royal Victorian Hospital HREC, Western Institutional Review Board, or Wills Eye Hospital IRB) approved the study protocol at each site, and all patients provided written informed consent. The study is registered at ClinicalTrials.gov with the identifier NCT02087085.

The study was initiated in May 2014 and completed in March 2018. Patients were screened at 44 study centers in Australia, France, Germany, Italy, the United Kingdom, and the United States, and were enrolled and randomized at 41 of the study centers.

Patient Eligibility Criteria

Key inclusion criteria included men or women, aged $\geq$ 55 years, diagnosed with GA secondary to AMD in the study eye, as assessed with fundus autofluorescence (FAF) at screening and confirmed by the central reading center (CRC; GRADE Reading Center, University of Bonn Department of Ophthalmology). Areas of GA were funduscopically visible discrete pale areas characterized by a marked decrease in FAF intensity and loss of outer-retinal layers with choroidal signal hypertransmission, as assessed with spectral-domain OCT. The areas of atrophy in the study eye were required to be multifocal lesions characterized by the presence of banded or diffuse perilesional hyper-autofluorescence evident on FAF.[18] The total GA lesion area in the study eye was required to be > 1.25 mm^2 and ≤ 18 mm^2, and the distance between optic disc or peripapillary atrophy and GA lesions was required to be > 300 μm. Best-corrected visual acuity assessed using the standard ETDRS protocol was required to be 45 letters (~20/125 Snellen equivalent) or better in the study eye and 34 letters (~20/200 Snellen equivalent) or better in the fellow eye. Patients who participated in microperimetry assessments were required to have mean retinal sensitivity threshold reproducibility within 6 decibels (dB) in the study eye.[19]

Key exclusion criteria included absence of perilesional hyper-autofluorescence in the study eye; history or evidence of submacular surgery or other procedure for AMD in the study eye; use of any periocular or intravitreally injected therapy in the study eye within 3 months before screening; and history or current evidence of any medical condition that, in the opinion of the investigator, might affect the results of the study, or preclude the safe administration of study medication or the patient's adherence to scheduled study visits or safe participation in the study. Patients with history or evidence of choroidal neovascularization in either eye, or history or evidence of any concomitant retinal disease other than GA in the study eye that might confound the assessment of macular function and structure (e.g., diabetic retinopathy or pathologic myopia), were also excluded.

If both eyes were eligible for the study, the eye with the worse BCVA, or the right eye if the BCVA was the same in both eyes, was selected as the study eye. A complete list of the patient eligibility criteria is provided in Table S1 (available at www.ophthalmologyretina.org/).

Visit Schedule, Randomization, Intervention, and Masking

Study visits included a screening visit up to 22 days before the baseline visit; a second screening visit for patients who participated in microperimetry assessments; the baseline (day 1) visit with initial treatment; safety visits on day 7 and month 1; retreatment visits at months 3, 6, 9, 12, 15, 18, and 21; and follow-up visits after the active treatment period at months 24 and 30 (Fig 1). On day 1, enrolled patients were randomized in a 1:1 ratio to receive 400-μg Brimo DDS or sham treatment (control) in the study eye. The randomization was stratified by region (North America, Europe, and Australia) and by GA lesion area in the study eye (≤ 8 mm^2 vs. > 8 mm^2), as assessed by FAF examination at screening and quantified by the CRC. The randomization scheme was computer generated and provided by the study sponsor, and an automated interactive voice response system/interactive web response system was used to manage the treatment assignments.

The study treatments were administered every 3 months from day 1 to month 21. The Brimo DDS was administered by intravitreal injection through the pars plana with a single-use 25-gauge applicator system. For the sham treatment, a needleless applicator containing no study medication was pressed against the temporal bulbar conjunctiva. Patients, investigators who performed ocular assessments, study personnel involved in the collection of efficacy data, and the CRC personnel were masked to the study treatment assignment.

Outcome Measures

The primary efficacy endpoint was the change from baseline in the GA lesion area in the study eye, assessed with FAF, at month 24. The GA lesion area in the study eye was assessed with FAF and quantified by the CRC at baseline and months 6, 12, 18, 24, and 30. A standardized procedure was used to obtain FAF images using the confocal scanning laser ophthalmoscopy capability of the Heidelberg Spectralis spectral-domain–OCT platform (Heidelberg Engineering). The scaling of the acquired images was corrected for corneal curvature and assessed using a keratometer or topographer

at the investigator's discretion. RegionFinder software (Heidelberg Engineering) was used to quantify the GA area on FAF images. The GA lesion area was also assessed with spectral-domain OCT in the study eye and by FAF in the fellow eye at baseline and months 6, 12, 18, 24, and 30.

Secondary efficacy outcome measures included standard BCVA (at 4 months) assessed in both eyes using the ETDRS visual acuity protocol, and low-luminance BCVA (at 4 months) assessed in both eyes with the same procedure using a 2.0 log unit neutral density filter. Standard and low-luminance BCVA was assessed at all visits except the second screening visit and the day 7 safety visit.

Microperimetry under scotopic conditions with dark adaptation was performed at selected sites using a Nidek MP-1S microperimeter (Nidek Inc), and images were evaluated by the CRC. Retinal sensitivity thresholds in the study eye were measured using a grid with 56 stimulus points at baseline and months 6, 12, 18, 24, and 30. One of 3 neutral density filters (0, 1.0, or 2.0) was used to increase the dynamic range of the instrument. In addition, at selected sites, patients assigned to Brimo DDS treatment had blood samples taken at baseline (predose), day 7, month 1, and month 3 (before the month 3 dose) for the determination of plasma brimonidine concentrations.

Safety measures included treatment-emergent adverse events (AEs; events with onset or worsening after the first study treatment), standard BCVA, complete ophthalmic examinations, postinjection assessments, and DDS assessments on indirect ophthalmoscopy or biomicroscopy. The DDS assessments were conducted by an unmasked investigator at day 7 and all subsequent visits. These assessments included the number of whole implants and implant fragments, implant size (recorded as $\leq$ 25%, 26%−50%, 51%−100%, or $>$ 100% of initial size), and the implant load (a composite measure determined by the number of whole implants and implant fragments and their size ranges), expressed as a proportion of the original DDS implant size.

Statistical Analyses

All statistical analyses were conducted using SAS Version 9.3 or newer software (SAS Institute Inc) and used observed values with no imputation for missing values. An interim analysis, when 50% of patients had either completed the month 18 visit or exited early, was planned. Because the study was terminated as a result of the interim analysis (details are provided in the results section), the results of the interim analysis are presented. Efficacy outcomes were evaluated in the modified intent-to-treat population of all randomized and treated patients with baseline and $\geq$ 1 postbaseline assessment of the GA lesion area by FAF. Safety outcomes were evaluated in the safety population of all patients who received $\geq$ 1 administration of study treatment, based on the actual treatment received.

Analyses of change from baseline in the GA lesion size on FAF used the area of the lesion (expressed in mm^2) and the effective radius of the lesion, which was calculated as the square root of the GA lesion area divided by π (and expressed in mm). Changes from baseline in GA lesion area and effective radius at months 6, 12, 18, 24, and 30 were analyzed with mixed-effects model for repeated measures (MMRM) models. The MMRM models included treatment, study region (North America, Europe, and Australia), visit, and treatment-by-visit interaction as factors, as well as baseline value and baseline value-by-visit interaction as covariates. A compound symmetry covariance structure shared across treatment groups was used to model the within-patient errors. The Kenward−Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

A prespecified subgroup analysis using similar MMRM models was conducted to evaluate whether the effects of Brimo DDS were observed sooner in patients with larger baseline lesions ($\geq$ 4.5 mm^2 vs. $<$ 4.5 mm^2). For this analysis, the median baseline value of the GA lesion area (4.5 mm^2) was used as the cutoff for larger versus smaller lesion size.

Calculations of mean retinal sensitivity included a numeric correction for the neutral density filter used in the microperimetry assessment. For this correction, values of 0, 10, and 20 dB were added to the recorded threshold sensitivities obtained with use of 0.0, 1.0, and 2.0 neutral density filters, respectively.

Changes from baseline in retinal sensitivity and standard and low-luminance BCVA were analyzed with MMRM models that included treatment, study region, visit, and treatment-by-visit interaction as factors, as well as baseline value and baseline value-by-visit interaction as covariates. An unstructured covariance structure shared across treatment groups was used to model the within-patient errors.

Other outcome measures, including assessments of residual DDS implant in the study eye, plasma brimonidine concentrations, and retinal sensitivity, were summarized with descriptive statistics by visit. Implant load was calculated as the sum of the midpoint value for size (relative to initial implant size) of all whole implants and implant fragments present; the midpoint value used was 12.5% for a recorded size of $\leq$ 25%, 37.5% for a recorded size of 26% to 50%, 75% for a recorded size of 51% to 100%, and 215% (based on in vitro data, AbbVie on file) for a recorded size of $>$ 100%.

The planned enrollment was approximately 300 patients (150 per treatment group) with an anticipated dropout rate of 20%. A sample size of 240 patients at month 24 (120 per treatment group) was estimated to provide 90% power to detect a 25% reduction in the rate of GA lesion growth in the Brimo DDS group relative to sham at month 24, using a 2-sided t test and an α level of 0.05, and assuming a GA lesion growth rate of 2.8 mm^2 over 24 months in the sham group and a common standard deviation (SD) for the GA lesion growth rate of 1.65 mm^2.

Results

A total of 310 patients were enrolled and randomized to study treatment: 154 to Brimo DDS 400 μg treatment and 156 to sham treatment. All randomized patients received the assigned study treatment and were included in the safety analyses. Among all randomized patients, 303 (97.7%) were included in the modified intent-to-treat population for efficacy analyses. The mean age of patients in the modified intent-to-treat population was 76.9 years, 99.7% of the patients were White, and 62.4% were women. Baseline demographics and disease characteristics were well balanced between the treatment groups (Table 2).

The study was terminated early by the study sponsor at the completion of the planned interim analysis, which was conducted after 50% of patients had completed the month 18 visit or exited early. The reason for the early termination of the study was the slow progression rate ($\sim$ 1.6 mm^2/year) in the enrolled population. At the time of the study termination, all enrolled patients remaining in the study had completed the month 12 visit, and the month 24 primary endpoint visit had been completed by 82 (53.2%) and 85 (54.5%) patients in the Brimo DDS and sham groups, respectively (Fig 2).

Study completion rates were low (22.1% [34/154] in the Brimo DDS group and 25.6% [40/156] in the sham group) primarily because of the early termination of the study (Fig 2). The mean (SD) study duration was 686 (194) days for the Brimo DDS group and 690 (189) days for the sham group. The mean (SD) number of study treatments received by patients was 6.6 (1.8) in the Brimo DDS group and 6.9 (1.6) in the sham group.

Table 2. Baseline Patient Characteristics (mITT Population)

Characteristic	Brimo DDS (N = 149)	Sham (N = 154)
Age, mean (SD), yrs	76.8 (7.99)	77.0 (7.27)
Range	55–98	55–98
≥ 75 yrs, n (%)	99 (64.4)	199 (65.7)
Gender, n (%)		
Female	98 (65.8)	91 (59.1)
Male	51 (34.2)	63 (40.9)
Race, n (%)		
White	148 (99.3)	154 (100)
Black or African American	1 (0.7)	0 (0)
GA lesion area* in the study eye, mean (SD), mm^2	5.16 (3.70)	5.47 (3.59)
Range	0.581–23.415	0.935–17.302
> 8 mm^2, n (%)	27 (18.1)	33 (21.4)
Multifocal lesion, n (%)	154 (100)	149 (100)
Standard BCVA in study eye, mean (SD), ETDRS letters	70.3 (10.6)	69.7 (10.3)
Snellen equivalent	~ 20/40	~ 20/40
Low-luminescence BCVA in the study eye, mean (SD), ETDRS letters	42.9 (18.3)	40.7 (16.1)

BCVA = best-corrected visual acuity; Brimo DDS = 400-μg Brimonidine Drug Delivery System Generation 2; GA = geographic atrophy; mITT = modified intent-to-treat; SD = standard deviation.
*Assessed by fundus autofluorescence. Fifteen patients had a baseline total lesion area outside the permitted range of 1.25–18 mm^2 (< 1.25 mm^2 for 7 in the Brimo DDS group and 6 in the sham group, > 18 mm^2 for 2 in the Brimo DDS group).

Efficacy

Geographic atrophy area change from baseline at month 24 (primary endpoint, least squares mean [standard error]) was 3.24 (0.13) mm^2 in the Brimo DDS group (n = 84) and 3.48 (0.13) mm^2 in the sham group (n = 91); the GA area change from baseline at month 24 was reduced by 0.25 mm^2 (7%) in the Brimo DDS group compared with sham (P = 0.150). At month 30, the number of study participants with data was much smaller, but the reduction in the GA progression rate with Brimo DDS was statistically

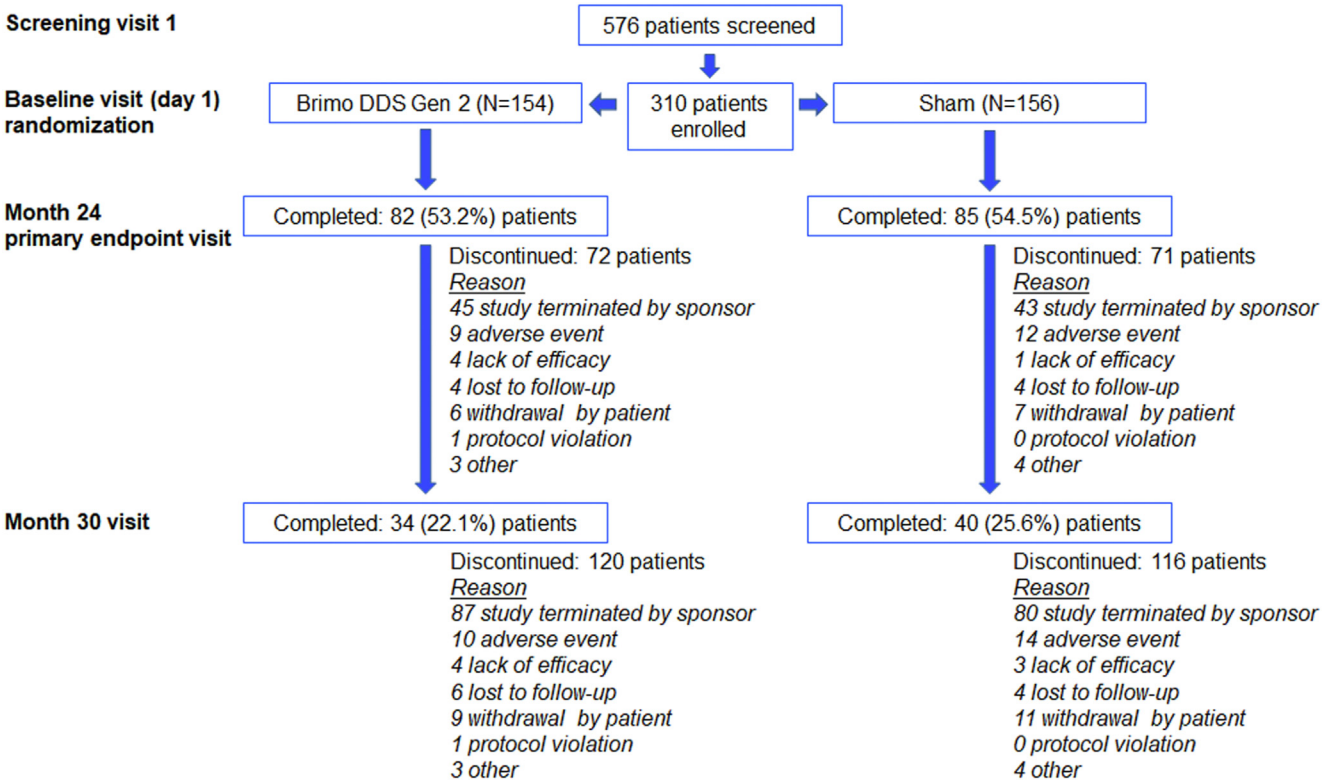

Figure 2. Patient flow diagram. The study began enrollment in May 2014, and the last patient visit was in March 2018. Brimo DDS Gen 2 = 400-μg Brimonidine Drug Delivery System Generation 2.

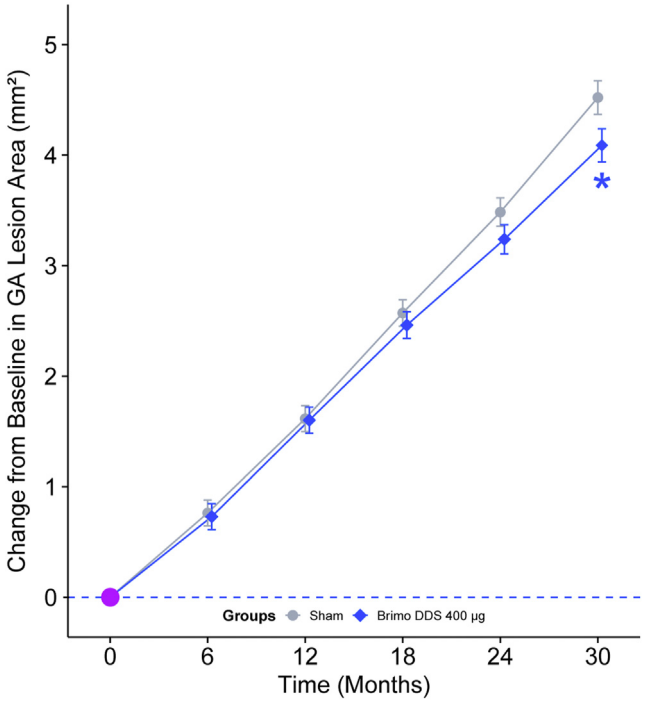

Figure 3. Primary efficacy measure of the change from baseline in geographic atrophy (GA) lesion area in the study eye assessed by fundus autofluorescence. Data shown are least squares means ± standard error from a mixed-effects model for repeated measures. The n at baseline and months 6, 12, 18, 24, and 30 was 149, 145, 138, 125, 84, and 49 in the 400-µg Brimonidine Drug Delivery System Generation 2 (Brimo DDS) group and 154, 151, 139, 126, 91, and 46 in the sham group, respectively. *$P = 0.033$ versus sham.

significant. The GA area change from baseline at month 30 (4.09 [0.15] mm^2 in the Brimo DDS group [n = 49] and 4.52 [0.15] mm^2 in the sham group [n = 46]) was reduced by 0.43 mm^2 (10%) in the Brimo DDS group compared with sham ($P = 0.033$) (Fig 3).

Results of the analysis of the change from baseline in the effective radius of the GA lesion were consistent (Fig 4). The effective radius of the GA lesion change from baseline was reduced by 0.034 mm (9%) in the Brimo DDS group compared with sham at month 24 ($P = 0.07$) and by 0.042 mm (9%) in the Brimo DDS group compared with sham at month 30 ($P = 0.07$).

The growth of the GA lesion area was faster in the subgroup of patients with a baseline GA lesion area of 4.5 mm^2 (the median baseline value) or larger than in the subgroup of patients with smaller lesions (Fig 5). The treatment effects of Brimo DDS in the subgroup with larger lesions (0.30 mm^2 [7%] and 0.49 mm^2 [9%] reductions in the GA lesion area change from baseline compared with sham at months 24 and 30, respectively) were larger than those in the total study population with respect to the absolute differences in the GA lesion area change from baseline; however, they were similar to those in the total study population with respect to the percentage reduction in the GA progression rate. The Brimo DDS had less effect on lesion growth in patients with a baseline GA lesion area smaller than the median value (< 4.5 mm^2) (Fig 5). Within this subgroup, the GA lesion area change from baseline was reduced by 0.13 mm^2 (5%) with Brimo DDS treatment compared with sham at month 24 and by 0.22 mm^2 (6%) with Brimo DDS treatment compared with sham at month 30. Results of the subgroup analysis of the change from baseline

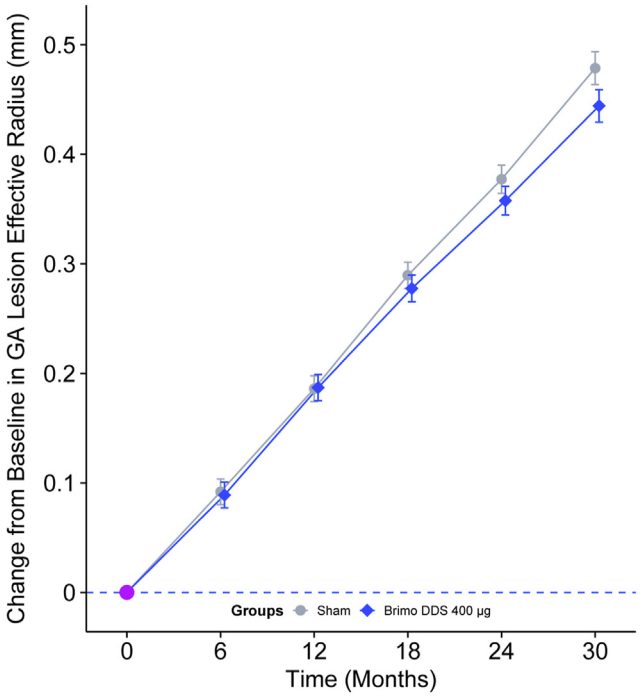

Figure 4. Change from baseline in geographic atrophy (GA) lesion effective radius in the study eye. Data shown are least squares means ± standard error from a mixed-effects model for repeated measures. Brimo DDS = 400-µg Brimonidine Drug Delivery System Generation 2.

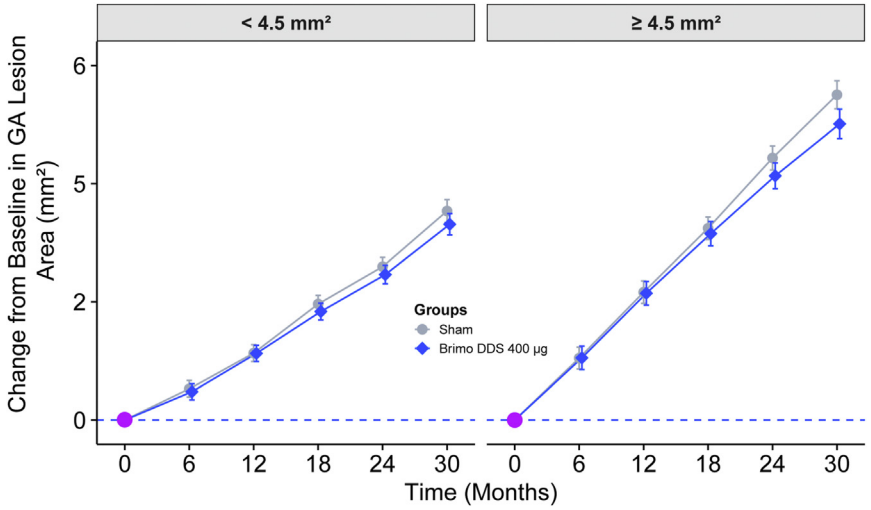

Figure 5. Change from baseline in geographic atrophy (GA) lesion area in the study eye for the subgroups of patients with baseline GA lesion area of < 4.5 mm^2 and ≥ 4.5 mm^2. Data shown for each subgroup are least squares means ± standard error from a mixed-effects model for repeated measures. Brimo DDS = 400-µg Brimonidine Drug Delivery System Generation 2.

in the effective radius of the GA lesion area were consistent, with larger treatment effects of Brimo DDS relative to sham observed in patients with a baseline GA lesion area of ≥ 4.5 mm^2 (Fig 6).

In secondary efficacy analyses, standard BCVA in the study eye decreased progressively in both treatment groups over the course of the study (~2 to 3 lines of vision loss by month 30) (Table S3, available at www.ophthalmologyretina.org/). Treatment with Brimo DDS did not slow the progression of vision loss. Similarly, low-luminance BCVA in the study eye decreased progressively during the study in both treatment groups (~ 2 lines of vision loss by month 30), with no effect of Brimo DDS treatment on this measure (Table S4, available at www.ophthalmologyretina.org/).

Exploratory MMRM analysis of the change from baseline in the GA lesion area in the study eye as assessed with spectral-domain OCT (Fig S7, available at www.ophthalmologyretina.org/) showed numerically reduced GA lesion area growth in the Brimo DDS group compared with the sham group throughout the study, but none of the differences between treatment groups were statistically significant. The difference between treatment groups was the largest at month 30, when GA lesion area growth was reduced by 0.43 mm^2 (10%) in the Brimo DDS group compared with sham ($P = 0.202$). An MMRM subgroup analysis of growth in the GA lesion area on spectral-domain OCT for the subgroups of patients with baseline GA lesion area of ≥ 4.5 mm^2 and < 4.5 mm^2 was consistent with the subgroup analysis of lesion area growth based on FAF. In the subgroup of patients with baseline GA lesion area of ≥ 4.5 mm^2, the growth of GA lesion area was significantly reduced by 1.37 mm^2 (25%) in the Brimo DDS group compared with the sham group at month 30

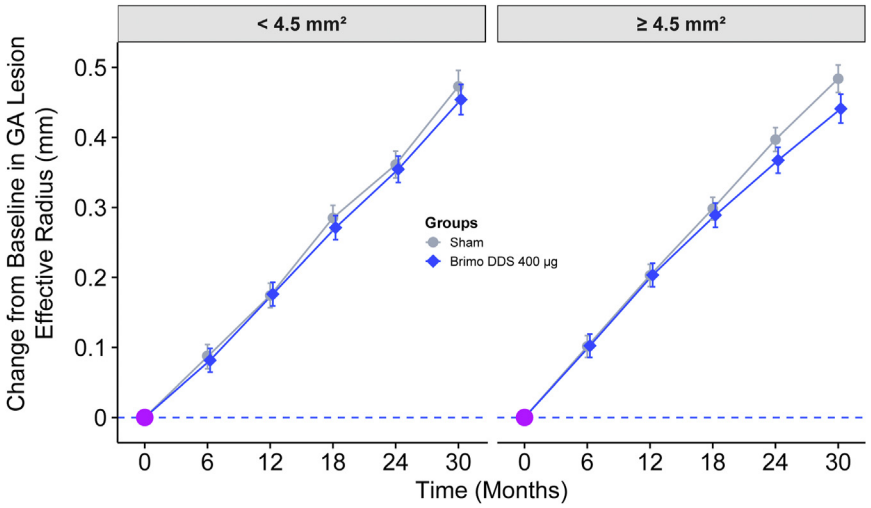

Figure 6. Change from baseline in geographic atrophy (GA) lesion effective radius in the study eye for the subgroups of patients with baseline GA lesion area of < 4.5 mm^2 and ≥ 4.5 mm^2. Data shown for each subgroup are least squares means ± standard error from a mixed-effects model for repeated measures. Brimo DDS = 400-µg Brimonidine Drug Delivery System Generation 2.

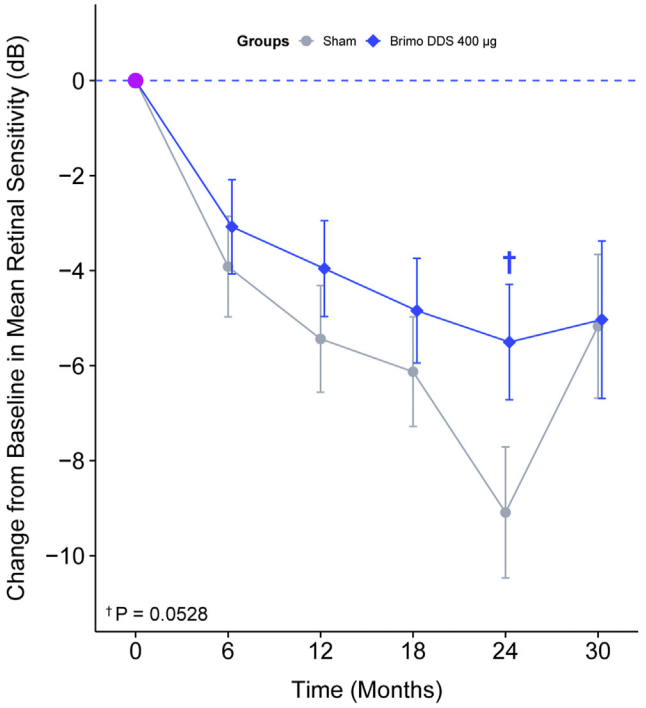

Figure 8. Change from baseline in retinal sensitivity in the study eye. Data shown are least squares means ± standard error from a mixed-effects model for repeated measures. The n at baseline and months 6, 12, 18, 24, and 30 was 50, 36, 34, 29, 24, and 12 in the 400-µg Brimonidine Drug Delivery System Generation 2 (Brimo DDS) group and 51, 38, 31, 28, 19, and 13 in the sham group, respectively. †$P = 0.0528$ versus sham. dB = decibels.

($P = 0.007$). There were no significant differences between treatment groups in GA lesion area change from baseline on spectral-domain OCT in the subgroup of patients with baseline GA lesion area of < 4.5 mm^2.

Microperimetry was performed at selected sites in 101 patients. Exploratory analysis of the change from baseline in retinal sensitivity in the study eye showed a loss in retinal sensitivity over time in both treatment groups. However, the loss in retinal sensitivity was consistently less in the Brimo DDS group compared with the sham group, and the difference between groups bordered on statistical significance at month 24 ($P = 0.053$) (Fig 8).

Safety

The overall incidence of any AE was similar between the treatment groups (79.9% in the Brimo DDS group and 80.8% in the sham group) (Table 5). Treatment-emergent AEs led to the discontinuation of 6.5% of patients in the Brimo DDS group and 9.0% of patients in the sham group; the adverse events most commonly leading to study discontinuation were neovascular AMD in the Brimo DDS group (n = 2) and choroidal neovascularization in the sham group (n = 5). The incidence of ocular AEs was higher in the Brimo DDS group (62.3%) than in the sham group (45.5%). Almost all treatment-related AEs were ocular; these AEs most commonly were related to the injection procedure (Table 5).

Table 5. Incidence of AEs (Safety Population)

Parameter, n (%)	Brimo DDS (N = 154)	Sham (N = 156)
Any AE	123 (79.9)	126 (80.8)
Ocular	96 (62.3)	71 (45.5)
Nonocular	93 (60.4)	107 (68.6)
Treatment-related AE*	67 (43.5)	24 (15.4)
Ocular	67 (43.5)	24 (15.4)
Related to implant/study drug	26 (16.9)	1 (0.6)
Related to the injection procedure	38 (24.7)	18 (11.5)
Related to other study procedure	24 (15.6)	11 (7.1)
Nonocular	4 (2.6)	2 (1.3)
Serious AE	48 (31.2)	37 (23.7)
Ocular	7 (4.5)	2 (1.3)
Nonocular	44 (28.6)	35 (22.4)
Death†	5 (3.2)	6 (3.8)
Discontinuation due to AE	10 (6.5)	14 (9.0)

AE = treatment-emergent adverse event; Brimo DDS = 400-µg Brimonidine Drug Delivery System Generation 2.
*AE that was deemed related to the study product or study procedures by the investigator.
†No death was considered by the investigator to be related to treatment.

Most of the serious AEs were nonocular (Table 5). There were 5 deaths in the Brimo DDS group and 6 deaths in the sham group; all were considered unrelated to the study treatment. However, there were 3 serious ocular AEs in the Brimo DDS group that were deemed by the investigator to be treatment-related: 2 vitreous hemorrhages and 1 retinal tear. All were judged to be related to the injection procedure and resolved during the study without any changes made in the study treatment administration.

The most common ocular AEs in study eyes were vitreous floaters and conjunctival hemorrhage (Table 6). Rates of neovascular AMD or choroidal neovascularization events in study eyes were similar between the treatment groups (4.5% and 5.1% in the Brimo DDS and sham groups, respectively). There were no reports of endophthalmitis in either group.

Assessments of the DDS showed that multiple administrations of Brimo DDS Gen 2 did not lead to accumulation of implant material in study eyes. Implant load (a composite measure of the total number and size of implant remnants) reached a steady state by month 1, at approximately 150% the initial size of 1 implant (Fig 9). The steady-state implant load was > 100% because the implant swells after administration as it biodegrades.

Pharmacokinetics

A total of 57 patients had ≥ 1 measurement of plasma brimonidine concentrations after treatment with Brimo DDS 400 µg. Brimonidine concentrations were quantifiable in all 57 patients at ≥ 1 timepoint. Mean brimonidine plasma concentrations at each timepoint are summarized in Table 7. Throughout the study, systemic drug exposure was low. The mean (SD) maximum concentration of brimonidine in plasma after intravitreal Brimo DDS administration was 1.82 (1.07) pg/ml, and the highest concentration measured in any individual at any timepoint (5.92 pg/ml) was almost 2 orders of magnitude lower than the concentration of

Table 6. Ocular AEs Reported in the Study Eye of > 2% of Patients in the Either Treatment Group (Safety Population)

AE, n (%)	Brimo DDS (N = 154)	Sham (N = 156)
Vitreous floaters	29 (18.8)	1 (0.6)
Conjunctival hemorrhage	21 (13.6)	10 (6.4)
Visual impairment	12 (7.8)	4 (2.6)
Eye pain	11 (7.1)	9 (5.8)
Visual acuity reduced	9 (5.8)	4 (2.6)
Dry eye	8 (5.2)	6 (3.8)
Ocular discomfort	8 (5.2)	1 (0.6)
Cataract	6 (3.9)	5 (3.2)
Vitreous hemorrhage	6 (3.9)	1 (0.6)
Vision blurred	5 (3.2)	3 (1.9)
Blepharitis	4 (2.6)	2 (1.3)
Conjunctival hyperemia	4 (2.6)	3 (1.9)
Eye irritation	4 (2.6)	3 (1.9)
Eye pruritus	4 (2.6)	2 (1.3)
Neovascular AMD	4 (2.6)	1 (0.6)
Choroidal neovascularization	3 (1.9)	7 (4.5)
Punctate keratitis	3 (1.9)	4 (2.6)

AE = treatment-emergent adverse event; AMD = age-related macular degeneration; Brimo DDS = 400-μg Brimonidine Drug Delivery System Generation 2.

brimonidine producing half-maximal effect at α2 adrenergic receptors.[20] The time to maximum plasma brimonidine concentration generally ranged from 1 to 3 months.

Discussion

This study evaluated the safety and efficacy of Brimo DDS Gen 2 400 μg on retinal structure and visual function in patients with GA secondary to AMD. The primary efficacy measure was GA lesion area in the study eye assessed with FAF. Fundus autofluorescence imaging has become the method of choice to evaluate in GA in large clinical trials.[21]

The Brimo DDS was well tolerated in the 154 patients who received active treatment. Systemic drug exposure was low, and treatment-related AEs were mostly ocular and did not lead to study discontinuation. Accumulation of implants was not seen with multiple administrations of Brimo DDS Gen 2, and implant load (a composite measure of the total number of implant remnants and their sizes) reached a steady state by month 1, at approximately 150% the size of 1 implant.

The study was terminated early because of the slow progression rate (~1.6 mm^2/year) in the enrolled population. This progression rate was much lower than the ~3.1 mm^2/year progression rate observed in the combined second and highest tertiles of baseline GA lesion area for sham-treated eyes in the phase IIa study of Brimo DDS[16] and also lower than the 1.85 mm^2/year progression rate observed in the Geographic Atrophy Progression (GAP) study of the natural history of GA in AMD.[22] Nonetheless, reductions in the GA progression rate of 7% and 10% were observed at months 24 and 30, respectively, for the 400-μg Brimo DDS-treated group compared with sham. The difference at month 30 was statistically significant ($P = 0.033$) but not necessarily clinically significant, and only 24% of participants had reached the month 30 timepoint when the study was terminated. A 10% reduction in the GA progression rate (not statistically significant) was also observed when the GA area was measured by spectral-domain OCT.

The relationship between GA lesion area and the rate of GA area progression has been well studied. The Age-Related Eye Disease Study showed that patients with larger lesions at baseline progress at a more rapid rate.[23] The GAIN study, a prospective natural history study of GA secondary to AMD, similarly demonstrated a positive relationship between the baseline area of atrophy and GA progression.[24]

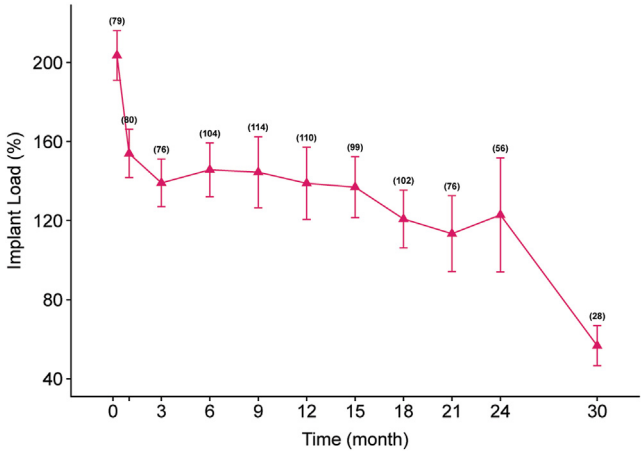

Figure 9. Implant load over time in study eyes in the 400-μg Brimonidine Drug Delivery System Generation 2 treatment group. Implant load for each patient was defined as the summation of the size of all whole implants and implant fragments present, expressed as a percentage of the initial size of an implant. In the calculation, size of each implant/fragment was set to 215% if the recorded size was > 100%, 75% if the recorded size was 51% to 100%, 37.5% if the recorded size was 26% to 50%, and 12.5% if the recorded size was ≤ 25%. Data shown are means ± standard error of the mean. The number of patients with implant assessment at each visit is shown in parentheses.

Table 7. Brimonidine Plasma Concentrations after Intravitreal Administration of Brimo DDS 400 μg (Gen 2)

Visit	N	Mean ± SD (pg/ml)	Minimum/Maximum (pg/ml)
Baseline (before dose)	50	BLQ	BLQ/BLQ
Day 7	54	0.137 ± 0.092	BLQ/0.382
Month 1	52	1.47 ± 1.09	0.384/5.92
Month 3	49	1.40 ± 0.83	BLQ/3.78

BLQ = beneath the limit of quantitation (< 0.1 pg/ml); Brimo DDS = Brimonidine Drug Delivery System; Gen = generation; SD = standard deviation.

In clinical trials, an adequate rate of progression is needed in sham-treated patients in order to demonstrate a benefit of the active treatment in decreasing progression. In the FILLY phase II study of the complement C3 inhibitor pegcetacoplan in patients with GA secondary to AMD, the baseline mean GA lesion area ranged from 8.0 to 9.0 mm^2 among the treatment groups, the square root GA lesion area progression rate was 0.35 mm/year in the pooled sham group at month 12, and a significant 29% reduction in the square root GA lesion growth rate was demonstrated at month 12 with monthly pegcetacoplan compared with sham.[25] In subsequent phase III studies of pegcetacoplan (OAKS [NCT03525600] and DERBY [NCT03525613]), the baseline mean GA lesion area across treatment groups ranged from 8.12 to 8.30 mm^2 in OAKS and 8.24 to 8.37 mm^2 in DERBY, GA lesion area progression rates in the sham groups at month 12 were approximately 2.0 mm^2/year in each study, and monthly pegcetacoplan met the primary endpoint of reduction in lesion growth at month 12 in OAKS (21% reduction in lesion growth compared with sham) and failed to meet the primary endpoint in DERBY (12% reduction in lesion growth compared with sham) (Goldberg R, Heier J, Wykoff C, et al. Efficacy of intravitreal pegcetacoplan in patients with geographic atrophy (GA): 18-month results from the phase 3 OAKS and DERBY studies. Paper presented at the Association for Research in Vision and Ophthalmology Annual Meeting; May 2, 2022; Denver, CO). In the phase II/III GATHER1 study, the baseline mean GA lesion area ranged from 7.33 to 7.90 mm^2 across treatment groups; the GA lesion area progression rates at month 12 were 2.77 and 2.29 mm^2/year in the sham groups at month 12 (square root GA lesion area progression rates were 0.402 and 0.444 mm^2/year), and monthly treatment with the complement C5 inhibitor avacincaptad pegol 2 mg and 4 mg demonstrated efficacy in reducing the GA growth rate over 12 months compared with sham.[26]

A positive association between baseline lesion area and GA progression was also observed in the phase IIa study of Brimo DDS.[16] In that study, the baseline mean lesion area ranged from 9.8 to 12.2 mm^2 across treatment groups.[16] A post hoc analysis was performed to evaluate the effect of Brimo DDS in patients with varying lesion burden at baseline, comparing the treatment effect for patients with small (tertile 1: < 6 mm^2) versus medium (tertile 2: 6 to < 13 mm^2) or large (tertile 3: ≥ 13 mm^2) GA lesions. In patients with baseline lesion area of ≥ 6 mm^2 (combined tertiles 2 and 3), a statistically significant reduction in GA progression was observed (32% and 36% reduction in the progression of GA lesion area in the Brimo DDS 132- and 264-μg groups, respectively) at month 12.[16] The reduction in GA progression for patients with lesion sizes of ≥ 13 mm^2 at baseline (tertile 3) was 38% and 59% for the Brimo DDS 132- and 264-μg groups, respectively, at month 12.[16]

The mean baseline GA lesion size in this study (5.16 mm^2 in the Brimo DDS group and 5.47 mm^2 in the sham group) was smaller than in other study populations (where it ranged from 7.33−12.2 mm^2 across treatment groups),[16,25–27] likely accounting for the overall slow rate of progression observed. As in the phase IIa study, patients in this study with larger lesions at baseline demonstrated a faster rate of GA lesion growth, and a preplanned analysis showed that treatment effects were driven primarily by patients with baseline GA lesions of median size or larger (≥ 4.5 mm^2). Trends for treatment effects were similar when GA lesion area was measured by spectral-domain OCT.

In addition to the baseline lesion area, disease characteristics, including lesions with multiple areas of atrophy (i.e., multifocal lesions),[22,28] increased FAF outside GA lesions,[29] and extrafoveal lesions (compared with fovea involving lesions),[22] have been linked with more rapid lesion growth rates. In this study, patients with unifocal GA lesions, lesions in which the total lesion area was > 18 mm^2, and lesions without perilesional hyperfluorescence were excluded. It was expected that this reduction in lesion phenotypic variability would decrease the variability of lesion growth rates, thereby decreasing the sample size required to demonstrate a treatment effect in a study using GA lesion growth as the primary efficacy variable. However, the ability to detect a treatment effect depends on the magnitude of the lesion growth rate as well as its variability. Any reduction in the variability of lesion growth rate that was achieved by the reduction in lesion phenotypic variability was not sufficient to overcome the slow growth rate (resulting from the relatively small baseline lesion size; the study population mean lesion size of ∼5.3 mm^2 was approximately 50%−70% of the lesion size in other published studies[16,25–27]) and demonstrate a statistically significant treatment effect for the selected sample size and study duration. The exclusion of patients with lesion area > 18 mm^2 in this study likely contributed to the observed small mean baseline lesion area and slow progression rate, but not having an upper limit on GA size would have allowed GA lesions to extend beyond the FAF image, interfering with growth monitoring.

No beneficial effect of Brimo DDS treatment on standard BCVA was observed. However, standard BCVA may not be a sensitive measure of visual function in patients with GA related to AMD.[30] In the Age-Related Eye Disease Study, initial GA lesions typically spared the fovea, and the median time from diagnosis of any GA to development of central GA was 2.5 years. There was little loss in visual acuity before central (foveal) GA involvement, and after central GA involvement, visual acuity declined at a slow

rate over a period of years.[23] Consistent with the Age-Related Eye Disease Study findings, a retrospective study of outcomes in patients with bilateral GA and no history of choroidal neovascularization reported a median time from diagnosis of GA to legal blindness of 6.2 years.[31] Therefore, in this study where patients on average had good BCVA (70 letters, 20/40) at baseline, loss in vision could be expected to be slow and variable, and a longer study duration would be needed to reliably measure treatment effects. Low-luminance BCVA, a more sensitive measure of early visual dysfunction in patients with GA secondary to AMD,[30] was also evaluated. There were no significant differences between the Brimo DDS and sham groups in the change from baseline in low-luminance BCVA.

Photoreceptor function was assessed with fundus-controlled perimetry, i.e., microperimetry, to allow evaluation of the relationship between functional and structural degeneration at precise locations of the retina. Microperimetry was evaluated in only a subset of patients, and the number of patients with data at later visits was further reduced because of the early study termination. Analysis of the microperimetry results showed numerically smaller changes in retinal sensitivity in the Brimo DDS group compared with the sham group at each timepoint, but none of the differences between the groups were statistically significant. Additional analysis evaluating the sensitivity of individual microperimetry points relative to their location on the lesion is underway and will be reported separately.

This study differed from the phase IIa study of Brimo DDS[16] in using both an improved formulation, which provides higher intraocular drug concentrations, and more frequent dosing. Disease characteristics also differed between the study populations—less than half of the study eyes had multifocal lesions in the phase IIa study, compared with 100% in this study. Both the baseline GA lesion area and the rate of lesion area growth were larger in the phase IIa study compared with this study. Nonetheless, the results of the studies were consistent in showing that any potential treatment effect of Brimo DDS was more likely to be observed in eyes with a larger GA lesion area at baseline.

A study limitation is that the planned interim analysis showed a slow rate of GA lesion progression, resulting in early termination of the study and insufficient power to detect a statistically significant effect on GA lesion growth in the primary efficacy endpoint. Furthermore, given the slow progression rate, the study duration was not sufficiently long to detect potential treatment effects on function (i.e., standard and low-luminance BCVA). Finally, in the microperimetry assessments, the limited dynamic range of the instrument necessitated use of neutral density filters and made analysis more difficult, especially when evaluating retinal sensitivity at stimulus points with dense scotomas. A more detailed evaluation of the microperimetry data is underway and will be reported separately.

Macular pigment-mediated quenching of FAF intensity in the fovea limits the ability of FAF imaging techniques to detect GA lesions in the central retina, and the use of multiple imaging approaches is needed to ensure accurate identification of foveal lesion boundaries assessed with FAF.[21,32] A strength of this study is that multimodal imaging methodologies (i.e., corneal curvature assessment to correct for magnification of the acquired FAF images, dilated fundus photography, and spectral-domain OCT) were used to support the accuracy of GA lesion identification assessed with FAF. An additional study strength is that safety-related factors did not contribute to the decision to terminate the study early.

The sham procedure used in this study and other studies of intravitreal treatments for GA (FILLY,[25] GATHER1,[26] and OAKS and DERBY [Goldberg R, et al. Presented at the Association for Research in Vision and Ophthalmology Annual Meeting; May 2, 2022; Denver, CO]) is an effective method of masking study participants to prevent bias in subjective outcome measures.[33] Placebo injections, which could potentially be more effective in masking, are avoided to decrease the risk of injection-related complications.[33] However, intraocular sham injection and surgical interventions have been shown to have protective effects on the retina in animal models of retinal disease, presumably because of growth factor release after the intervention.[34] Because the effects of placebo intravitreal injections on GA progression have not been investigated, it is possible that the intravitreal injection procedure used in the active treatment groups could have had an effect on the GA progression observed in the active treatment groups in this and the FILLY, GATHER1, and OAKS/DERBY studies.

This study was terminated early because of the lower-than-expected progression rate, and the development of Brimo DDS has been halted. Further development is not planned at this time. However, the study results suggest that a neuroprotective approach to GA should be considered in the future.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.html (Accessed March 1, 2023).

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study.

An institutional review board or independent ethics committee approved the study protocol at each site (Administrative Secretariat Independent Ethics Committee A.O.U. of Cagliari, Bellberry HREC, Chesapeake Research Review (Advarra), CESC of the Province of Padua, Ethics Committee of the IRCCS San Raffaele Hospital in Milan, Ethics Committee of Milan Area A, Ethics Committee of Milan Area B, Ethics Committee of the University Hospital of Bologna, Ethics Committee of the University Hospital of Tübingen, Ethics Committee of the University of Bonn, Hôpital Ambroise Paré Laboratoire d'Anatomopathologie, Intercompany Ethics Committee Molinette Hospital, NRES Committee London, Oregon Health and Science IRB, Royal Victorian Hospital HREC, Western Institutional Review Board, or Wills Eye Hospital IRB), and all patients provided written informed consent. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were used in this study.

Author Contributions: Conception and design: López

Data collection: Freeman, Bandello, Souied, Guymer, Garg, Chen, Rich, Holz, Patel

Analysis and interpretation: Freeman, Bandello, Souied, Guymer, Garg, Chen, Rich, Holz, Patel, Kim, López

Obtained funding: N/A.

Overall responsibility: Freeman, Bandello, Souied, Guymer, Garg, Chen, Rich, Holz, Patel, Kim, López

Abbreviations and Acronyms:
AE = treatment-emergent adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **Brimo DDS** = Brimonidine Drug Delivery System; **CRC** = central reading center; **dB** = decibels; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **Gen 1** = Generation 1; **Gen 2** = Generation 2; **MMRM** = mixed-effects model for repeated measures; **RPE** = retinal pigment epithelium; **SD** = standard deviation.

Keywords:
Age-related macular degeneration, Brimonidine, Geographic atrophy, Implant, Nonexudative.

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