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Holz, F.G.; Sadda, S.R.; Busbee, B.; Chew, E.Y.; Mitchell, P.; Tufail, A.; ... ; Chroma Spectri Study Investigators

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Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular Degeneration

Chroma and Spectri Phase 3 Randomized Clinical Trials

Frank G. Holz, MD; Srinivas R. Sadda, MD; Brandon Busbee, MD; Emily Y. Chew, MD; Paul Mitchell, MD, PhD; Adnan Tufail, MD, FRCOphth; Christopher Brittain, MBBS; Daniela Ferrara, MD, PhD; Sarah Gray, PhD; Lee Honigberg, PhD; Jillian Martin, MD; Barbara Tong, PhD; Jason S. Ehrlich, MD, PhD; Neil M. Bressler, MD; for the Chroma and Spectri Study Investigators

IMPORTANCE Geographic atrophy (GA) secondary to age-related macular degeneration is a leading cause of visual disability in older individuals. A phase 2 trial suggested that lampalizumab, a selective complement factor D inhibitor, reduced the rate of GA enlargement, warranting phase 3 trials.

OBJECTIVE To assess the safety and efficacy of lampalizumab vs sham procedure on enlargement of GA.

DESIGN, SETTING, AND PARTICIPANTS Two identically designed phase 3 double-masked, randomized, sham-controlled clinical trials, Chroma and Spectri, enrolled participants from August 28, 2014, to October 6, 2016, at 275 sites in 23 countries. Participants were aged 50 years or older, with bilateral GA and no prior or active choroidal neovascularization in either eye and GA lesions in the study eye measuring 2.54 to 17.78 mm² with diffuse or banded fundus autofluorescence patterns.

INTERVENTIONS Participants were randomized 2:1:2:1 to receive 10 mg of intravitreal lampalizumab every 4 weeks, sham procedure every 4 weeks, 10 mg of lampalizumab every 6 weeks, or sham procedure every 6 weeks, through 96 weeks.

MAIN OUTCOMES AND MEASURES Safety and efficacy assessed as mean change from baseline in GA lesion area at week 48 from centrally read fundus autofluorescence images of the lampalizumab arms vs pooled sham arms, in the intent-to-treat population and by complement factor I-profile genetic biomarker.

RESULTS A total of 906 participants (553 women and 353 men; mean [SD] age, 78.1 [8.1] years) were enrolled in Chroma and 975 participants (578 women and 397 men; mean [SD] age, 77.9 [8.1] years) were enrolled in Spectri; 1733 of the 1881 participants (92.1%) completed the studies through 48 weeks. The adjusted mean increases in GA lesion area from baseline at week 48 were 1.93 to 2.09 mm² across all groups in both studies. Differences in adjusted mean change in GA lesion area (lampalizumab minus sham) were −0.02 mm² (95% CI, −0.21 to 0.16 mm²; *P* = .80) for lampalizumab every 4 weeks in Chroma, 0.16 mm² (95% CI, 0.00–0.31 mm²; *P* = .048) for lampalizumab every 4 weeks in Spectri, 0.05 mm² (95% CI, −0.13 to 0.24 mm²; *P* = .59) for lampalizumab every 6 weeks in Chroma, and 0.09 mm² (95% CI, −0.07 to 0.24 mm²; *P* = .27) for lampalizumab every 6 weeks in Spectri. No benefit of lampalizumab was observed across prespecified subgroups, including by complement factor I-profile biomarker. Endophthalmitis occurred after 5 of 12 447 injections (0.04%) or in 5 of 1252 treated participants (0.4%) through week 48.

CONCLUSIONS AND RELEVANCE In Chroma and Spectri, the largest studies of GA conducted to date, lampalizumab did not reduce GA enlargement vs sham during 48 weeks of treatment. Results highlight the substantial and consistent enlargement of GA, at a mean of approximately 2 mm² per year.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT02247479](#) and [NCT02247531](#)

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Chroma and Spectri Study Investigators are listed at the end of this article.

Corresponding Author: Neil M. Bressler, MD, Johns Hopkins University School of Medicine, Maumenee 752, Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21287 (nmboffice@jhmi.edu).

Geographic atrophy (GA), an advanced form of age-related macular degeneration (AMD), is a leading cause of visual disability in elderly individuals,¹⁻³ with prevalence increasing substantially among those older than 75 years of age.^{2,3} No approved treatment slows or halts the progression of GA, or reverses the associated loss of macular tissue. In contrast, neovascular AMD, the other form of advanced AMD, is often treated successfully with intravitreal anti-vascular endothelial growth factor (anti-VEGF) medications.⁴⁻⁶ Similarly, the Age-Related Eye Disease Study⁷ and the Age-Related Eye Disease Study 2⁸ reported that dietary supplements reduce the risk of developing advanced neovascular AMD but have no apparent effect on GA.

Occurrence and enlargement of GA lesions can result in substantial visual disability.⁹⁻¹¹ Because lesions typically first appear outside the fovea,¹¹⁻¹³ testing of best-corrected visual acuity (BCVA) may inadequately assess functional impairment in individuals with preserved foveal function despite loss of pericentral macula.¹⁴ Other measures, including low-luminance visual acuity, reading speed, fundus-controlled microperimetry, and patient-reported outcomes, might assess impairment of visual function in patients with GA,^{15,16} but these measures were not extensively used in earlier GA trials.

Although the pathophysiology of GA is incompletely understood, dysregulation of the complement cascade, a component of the innate immune system,^{17,18} has been implicated in AMD^{19,20} and in GA specifically.²¹ Overall, genetic factors are estimated to account for 71% to 80% of the risk of advanced AMD,^{22,23} and common genetic variants near *CFH*, *CFI*, *C3*, and *C2/CFB*, which act in the alternative complement pathway, may account for 57% of known disease risk variants.²⁰

Given this genetic link, complement factor D was selected as a therapeutic target because it is the rate-limiting enzyme of the alternative complement pathway and is present in comparatively low abundance.²⁴⁻²⁶ Lampalizumab is an antigen-binding fragment of a humanized monoclonal antibody that is directed against, and inhibits, complement factor D.^{27,28} In a phase 2 trial, monthly intravitreal lampalizumab, 10 mg (n = 42), reduced the mean enlargement of GA lesion area from baseline to 18 months by 20% (80% CI, 4%-37%; *P* = .12) vs sham (n = 40).²⁹ In an exploratory subgroup analysis of carriers of the complement factor I (CFI) risk allele, monthly lampalizumab reduced the enlargement of GA by 44% vs sham.²⁹ No benefit was observed with lampalizumab treatment every 8 weeks.

To test phase 2 observations, we conducted 2 identically designed phase 3 randomized clinical trials, Chroma and Spectri, to assess the efficacy and safety of 10 mg of lampalizumab administered by intravitreal injection every 4 or 6 weeks vs sham treatment. These studies also prospectively investigated the prognostic and predictive diagnostic hypothesis of the CFI profile genetic biomarker. The 48-week primary outcome of these trials is presented herein.

Key Points

Question Does lampalizumab, a selective complement factor D inhibitor, reduce enlargement of lesions from geographic atrophy secondary to age-related macular degeneration?

Findings In 2 phase 3 randomized clinical trials (906 Chroma participants and 975 Spectri participants), no meaningful differences in the primary end point of mean change from baseline in geographic atrophy lesion area at week 48 were identified among eyes receiving 10-mg lampalizumab intravitreal injections either every 4 weeks or every 6 weeks vs sham.

Meaning These phase 3 trials showed that lampalizumab was ineffective as a treatment of geographic atrophy secondary to age-related macular degeneration.

Methods

The Chroma (trial protocol and statistical analysis plan are available in [Supplement 1](#)) and Spectri (trial protocol and statistical analysis plan are available in [Supplement 2](#)) studies were identically designed, phase 3 double-masked, multicenter, randomized, sham injection-controlled clinical trials at 131 (Chroma) and 144 (Spectri) sites in 23 countries. The studies adhered to the tenets of the Declaration of Helsinki³⁰ and were conducted in accordance with the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice³¹ and with applicable local, state, and federal laws. All sites received institutional review board or ethics committee approval before study initiation (eAppendix 1 in [Supplement 3](#)). Participants provided written informed consent. An independent data monitoring committee provided ongoing oversight. Key aspects of the study design are described herein and in eAppendix 2 in [Supplement 3](#).

Study Population

Eligible participants (eTable 1 in [Supplement 3](#)) were aged 50 years or older with bilateral GA secondary to AMD and no evidence of active or prior choroidal neovascularization (CNV) nor previous treatment for CNV in either eye. Key study eye inclusion criteria were a total GA lesion size from 2.54 to 17.78 mm² (1-7 disc areas) measured on blue-light fundus autofluorescence, as confirmed by the reading center; perilesional banded or diffuse autofluorescence patterns; and an Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA letter score of 49 or more (Snellen equivalent, 20/100 or better). Geographic atrophy lesions could be multifocal or unifocal, but at least 1 lesion had to be 1.27 mm² or larger (≥ 0.5 disc areas). In study eyes with a BCVA letter score of 79 or more (Snellen equivalent, 20/25 or better), at least 1 lesion was required within 250 μ m of the foveal center. One eye was selected as the study eye. If both eyes were eligible, the eye with the poorer visual function as determined by the investigator and the patient was selected, followed by the eye with the

larger GA lesion. Participants were also evaluated at screening for CFI-profile genetic biomarker status (eTable 2 in Supplement 3).

Randomization

Participants were randomly assigned 2:1:2:1 to receive 10 mg of lampalizumab every 4 weeks, sham procedure every 4 weeks, 10 mg of lampalizumab every 6 weeks, and sham procedure every 6 weeks, via an interactive voice and web response system. In the sham groups, the eye was prepped in a manner similar to lampalizumab groups to preserve masking, including subconjunctival anesthesia. However, instead of an actual intravitreal injection, only the hub of a syringe was placed against the planned injection site. For randomization, a permuted block design was used, and participants were stratified by CFI-profile biomarker status, baseline BCVA ETDRS chart Snellen equivalent (20/50 or better vs worse than 20/50), sex, and eligibility for microperimetry. Participant numbers were capped by CFI-profile biomarker status to achieve a 3:2 ratio for CFI-positive to CFI-negative participants. Sham arms were pooled for analysis, resulting in a 1:1:1 ratio for lampalizumab every 4 weeks, lampalizumab every 6 weeks, and sham.

Study Treatment and Assessments

Treatment was administered to the study eye at randomization (day 1) and every 4 or 6 weeks (± 5 days) thereafter through 44 weeks for groups receiving treatment every 4 weeks or 42 weeks for groups receiving treatment every 6 weeks, before week 48 primary efficacy assessments, continuing through 90 or 92 weeks per study design. Safety and ocular assessments, including BCVA, were performed at day 8 and at each subsequent visit on the same day as treatment. Verbatim descriptions of adverse events (AEs) were coded using *Medical Dictionary for Regulatory Activities*, version 20.0.³² Fundus images of both eyes at screening and specified visits were evaluated at the Doheny Image Reading Center (Los Angeles, California). Autofluorescence pattern eligibility was determined by the GRADE Reading Center (Bonn, Germany). Additional visual function assessments were performed as scheduled.

Outcomes

The primary efficacy outcome was mean change in GA lesion area from baseline to week 48 measured by fundus autofluorescence, graded at the reading center. Secondary efficacy outcomes assessing visual function were exploratory at week 48, with formal statistical testing planned at week 96. Safety outcomes were assessed through a summary of ocular and non-ocular AEs, deaths, results of serial electrocardiograms (selected participants), incidence of antidrug antibodies, and ocular assessments.

Statistical Analysis

For each study, a sample size of 188 CFI-positive participants per lampalizumab treatment arm and 94 CFI-positive participants per sham arm provided greater than 95% power to detect a difference in change in GA lesion area assuming a population difference of 1.45 mm² (approximately 40%

reduction relative to sham control) and an SD of 2.51 in the CFI-positive population. A sample size of 124 CFI-negative participants per lampalizumab treatment arm and 62 CFI-negative participants per sham arm provided 80% power to detect a difference assuming a population difference of 0.66 mm² (approximately 40% reduction relative to control) and an SD of 1.68 in the CFI-negative population (eTable 3 in Supplement 3). Calculations were based on 2-sided *t* tests at the $\alpha = .0495$ level with the assumption of a 15% dropout rate by week 48.

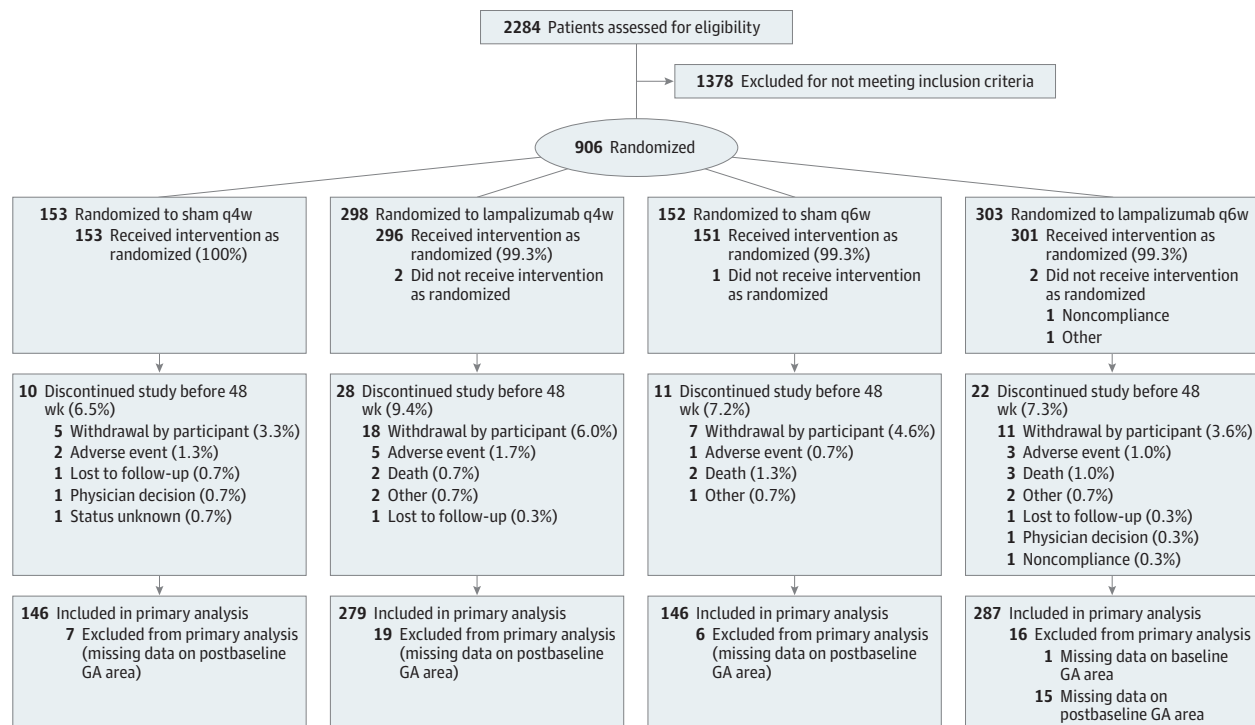
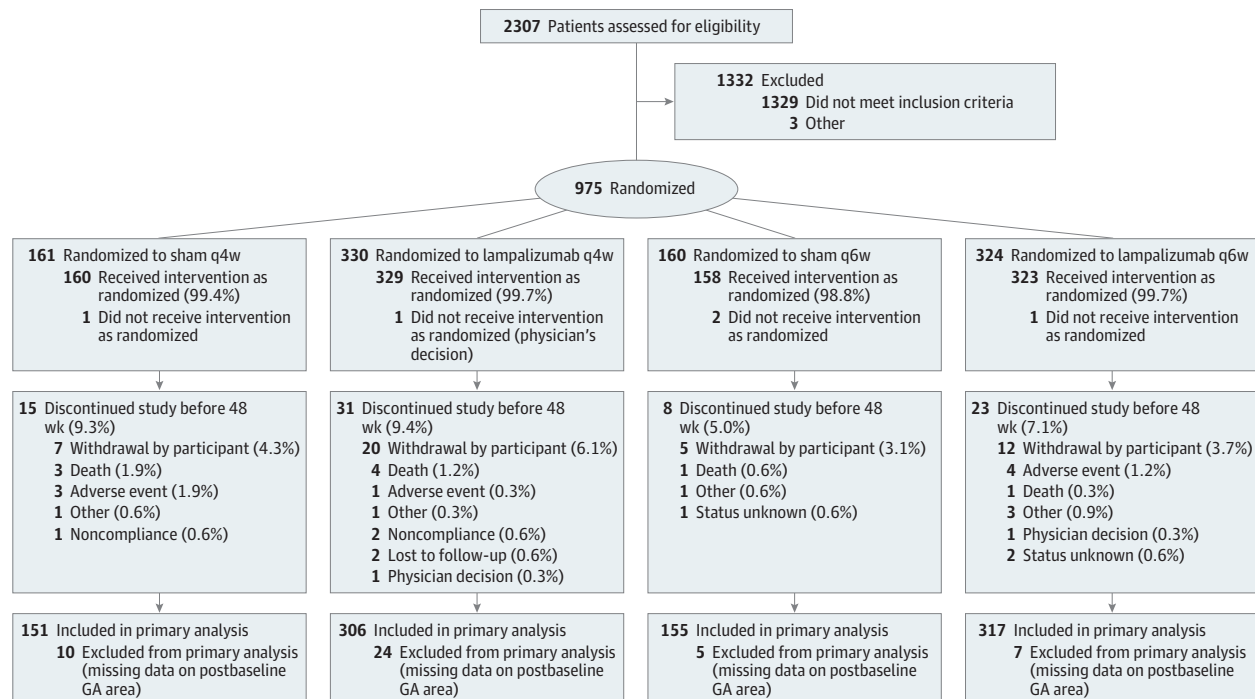
The primary efficacy analysis for comparison between each lampalizumab arm and the pooled sham arms was performed on the intent-to-treat population (all randomized participants) using a mixed effects model repeated-measures model based on available data to week 48, with no imputation for missing data. Change-from-baseline analysis excluded participants without a baseline measurement or at least 1 post-baseline measurement. The primary analysis adjusted for baseline GA lesion area, subfoveal vs nonsubfoveal location, and multifocal vs nonmultifocal configuration; CFI-profile biomarker status; BCVA (better than vs worse than 20/50 Snellen equivalent); and sex. Preplanned subgroup analyses by CFI-profile biomarker were performed similarly, except with the model fit separately for each biomarker group and without biomarker status as a covariate. Hypothesis testing was performed at a 2-sided $\alpha = .0496$ level to account for a 0.0001 nominal penalty for each of 4 planned independent data monitoring committee unmasked data reviews occurring before the primary analysis.

To assess robustness of the primary efficacy results, additional analyses included the growth slope of the GA lesion area over 48 weeks, the change from baseline in the square root of the GA lesion area at week 48, and the percentage change from baseline in the GA lesion area at week 48. Exploratory analyses by prespecified clinical subgroup were performed using mixed effects model repeated-measures analysis similar to the primary efficacy analysis, excluding baseline covariates not relevant for the particular subgroup. Safety analyses were performed on the population that received 1 or more doses of lampalizumab or sham, grouped according to actual treatment received regardless of assignment. Analyses were performed using SAS, version 9.4 (SAS Institute), separately by study and based on pooled data from Chroma and Spectri, which included an additional covariate adjustment for study, as appropriate.

Results

Between August 28, 2014, and October 6, 2016, 906 Chroma participants and 975 Spectri participants were randomized to receive sham every 4 weeks (153 Chroma participants; 161 Spectri participants), lampalizumab every 4 weeks (298 Chroma participants; 330 Spectri participants), sham every 6 weeks (152 Chroma participants; 160 Spectri participants), or lampalizumab every 6 weeks (303 Chroma participants; 324 Spectri participants) (Figure 1). The baseline demographic characteristics of the participants (Table 1 and eTables 4 and 5 in

Figure 1. CONSORT Flow Diagram for Chroma and Spectri Randomized Clinical Trials

A Chroma**B** Spectri

GA indicates geographic atrophy; q4w, every 4 weeks; and q6w, every 6 weeks.

Supplement 3) were well balanced across treatment groups (mean [SD] age of 78.0 [8.1] years, 1131 [60.1%] female, and 1827

[97.1%] white). The mean baseline GA lesion area was between 7.55 and 8.50 mm² across treatment groups. The mean

Table 1. Pooled Demographic and Baseline Characteristics of Chroma and Spectri Participants

Characteristic	Sham			Lampalizumab, 10 mg		
	q4w (n = 314)	q6w (n = 312)	Pooled (n = 626)	q4w (n = 628)	q6w (n = 627)	All (N = 1881)
Demographics						
Age, y						
Mean (SD)	78.1 (8.1)	78.0 (7.9)	78.0 (8.0)	77.4 (7.9)	78.5 (8.3)	78.0 (8.1)
Median (range)	78 (51-96)	78 (51-95)	78 (51-96)	78 (50-95)	80 (53-97)	79 (50-97)
Female sex, No. (%)	187 (59.6)	190 (60.9)	377 (60.2)	379 (60.4)	375 (59.8)	1131 (60.1)
White race, No. (%) ^a	306 (97.5)	302 (96.8)	608 (97.1)	608 (96.8)	611 (97.4)	1827 (97.1)
Tobacco use, No. (%)						
Never	153 (48.7)	136 (43.6)	289 (46.2)	293 (46.7)	290 (46.3)	872 (46.4)
Previous	147 (46.8)	155 (49.7)	302 (48.2)	295 (47.0)	295 (47.0)	892 (47.4)
Current	14 (4.5)	21 (6.7)	35 (5.6)	40 (6.4)	42 (6.7)	117 (6.2)
Study eye baseline characteristics						
GA area, ^b mm ²						
Mean (SD)	7.557 (3.884)	7.942 (4.025)	7.749 (3.956)	8.119 (3.904)	8.314 (4.249)	8.061 (4.044)
Median (range)	6.460 (1.58-17.56)	7.020 (2.61-30.56)	6.695 (1.58-30.56)	7.325 (2.54-17.74)	7.485 (2.29-22.19)	7.205 (1.58-30.56)
GA lesion contiguity, No. (%) ^b						
Multifocal	238 (75.8)	253 (81.1)	491 (78.4)	496 (79.0)	477 (76.2)	1464 (77.9)
Nonmultifocal	76 (24.2)	59 (18.9)	135 (21.6)	132 (21.0)	149 (23.8)	416 (22.1)
GA lesion location, No. (%) ^b						
Subfoveal	172 (54.8)	166 (53.2)	338 (54.0)	329 (52.4)	320 (51.1)	987 (52.5)
Nonsubfoveal	142 (45.2)	146 (46.8)	288 (46.0)	299 (47.6)	306 (48.9)	893 (47.5)
Hyperautofluorescence pattern, No. (%)						
Banded	12 (3.8)	11 (3.5)	23 (3.7)	22 (3.5)	35 (5.6)	80 (4.3)
Diffuse	301 (95.9)	301 (96.5)	602 (96.2)	605 (96.3)	591 (94.3)	1798 (95.6)
Not applicable	1 (0.3)	0	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
BCVA, mean (SD) letter score ^c	66.4 (10.0)	65.6 (9.6)	66.0 (9.8)	66.1 (9.8)	66.0 (9.9)	66.0 (9.9)
<64 (worse than 20/50)	115 (37.0)	118 (38.2)	233 (37.6)	253 (40.5)	247 (39.7)	733 (39.3)
≥64 (20/50 or better)	196 (63.0)	191 (61.8)	387 (62.4)	372 (59.5)	375 (60.3)	1134 (60.7)
LLVA, mean (SD) letter score ^d	36.6 (16.0)	36.2 (16.3)	36.4 (16.1)	36.5 (17.6)	36.0 (16.7)	36.3 (16.8)
Low-luminance deficit (BCVA – LLVA), mean (SD) letter score ^e	29.8 (16.1)	29.3 (15.9)	29.6 (16.0)	29.6 (16.3)	30.1 (15.7)	29.7 (16.0)

Abbreviations: BCVA, best-corrected visual acuity; GA, geographic atrophy; LLVA, low-luminance visual acuity; q4w, every 4 weeks; q6w, every 6 weeks.

^a Of the total study population, race/ethnicity was identified as 0.5% (n = 9) American Indian or Alaskan Native, 0.3% Asian (n = 5), 0.05% (n = 1) black or African American, 0.1% (n = 2) Native Hawaiian or other Pacific Islander, 0.2% (n = 4) multiple, and 1.8% unknown (n = 33).

^b For GA area, GA contiguity, and GA lesion location, there were 626 participants for the lampalizumab q6w arm.

^c For BCVA, there were 311 participants for the sham q4w arm, 309 for the sham

q6w arm, 625 for the lampalizumab q4w arm, and 622 for the lampalizumab q6w arm.

^d For LLVA, there were 304 participants for the sham q4w arm, 305 for the sham q6w arm, 609 for the lampalizumab q4w arm, and 603 for the lampalizumab q6w arm.

^e Low-luminance deficit = BCVA – LLVA; there were 303 participants for the sham q4w arm, 304 for the sham q6w arm, 609 for the lampalizumab q4w arm, and 603 for the lampalizumab q6w arm.

baseline BCVA letter score was between 65 and 66 (approximate Snellen equivalent, 20/50) in each group.

A total of 1733 of 1881 participants (92.1%) in Chroma and Spectri completed the first 48 weeks of the study, during which across treatment arms more than 76% of participants receiving treatment every 4 weeks received at least 12 injections (13 possible) and more than 85% of participants receiving treatment every 6 weeks received at least 8 injections (9 possible) (eAppendix 3 in Supplement 3).

After the Spectri primary analysis in September 2017, lampalizumab treatment was suspended for both studies at the sponsor's recommendation with the agreement of the chair of

the independent data monitoring committee because the apparent lack of efficacy did not warrant continued intravitreal injections.

Efficacy of Lampalizumab Treatment

GA Enlargement

At week 48, the adjusted mean increase in GA lesion area from baseline was 1.93 to 2.09 mm² across all groups in both studies (Table 2, Figure 2A, and eFigure 1A-B in Supplement 3). The differences in the adjusted mean change of the GA lesion area (lampalizumab minus sham) were –0.02 mm² (95% CI, –0.21 to 0.16 mm²; *P* = .80) for lampalizumab every 4 weeks in

Table 2. Change in GA Area From Baseline at Week 48 in Chroma and Spectri Pooled Intent-to-Treat Population^a

Measure	Sham	Lampalizumab, 10 mg	
	Pooled (n = 598)	q4w (n = 596)	q6w (n = 603)
Change from baseline in GA area at 48 wk, mm ²			
Adjusted mean (SE)	1.984 (0.043)	2.055 (0.043)	2.054 (0.043)
Difference in means (vs sham pooled)		0.071	0.070
95% CI		-0.049 to 0.191	-0.050 to 0.190
Relative reduction, %		-3.6	-3.5
P value		.25	.25
Rate of change in GA area (growth slope) from baseline to 48 wk, mm ² /365.25 d ^b			
Adjusted mean slope (SE)	1.998 (0.045)	2.076 (0.045)	2.085 (0.045)
Difference in slopes (vs sham pooled)		0.078	0.086
95% CI		-0.048 to 0.204	-0.039 to 0.212
Relative reduction, %		-3.9	-4.3
P value		.22	.18
Change from baseline in square root of GA area at 48 wk, mm			
Adjusted mean (SE)	0.342 (0.007)	0.349 (0.007)	0.352 (0.007)
Difference in means (vs sham pooled)		0.006	0.010
95% CI		-0.013 to 0.026	-0.009 to 0.029
Relative reduction, %		-1.8	-2.9
P value		.53	.32
% Change from baseline in GA area at 48 wk			
Adjusted mean (SE)	30.032 (0.856)	29.546 (0.859)	30.815 (0.853)
Difference in means (vs sham pooled)		-0.486	0.783
95% CI		-2.864 to 1.891	-1.586 to 3.153
Relative reduction, %		1.6	-2.6
P value		.69	.52

Abbreviations: GA, geographic atrophy; q4w, every 4 weeks; q6w, every 6 weeks.

^a Sample sizes shown in headers are the number of patients included in the mixed effects model repeated-measures analysis. All P values are 2-sided and calculated for the difference between means (lampalizumab minus sham).

^b For growth slope mixed effects model repeated-measures analysis, there were 626 participants for the sham pooled arm, 628 for the lampalizumab q4w arm, and 626 for the lampalizumab q6w arm.

Chroma, 0.16 mm² (95% CI, 0.00-0.31 mm²; $P = .048$ favoring sham) for lampalizumab every 4 weeks in Spectri, 0.05 mm² (95% CI, -0.13 to 0.24 mm²; $P = .59$) for lampalizumab every 6 weeks in Chroma, and 0.09 mm² (95% CI, -0.07 to 0.24 mm²; $P = .27$) for lampalizumab every 6 weeks in Spectri. Similarly, no benefit of lampalizumab over sham was observed in robustness assessments for the primary efficacy result (Table 2 and eTables 6 and 7 in Supplement 3). Furthermore, no benefit of lampalizumab over sham was observed for either CFI-profile biomarker subgroup (Figure 2 and eFigure 1 and eTable 8 in Supplement 3). Because baseline characteristics, follow-up, treatment adherence, and primary outcomes were similar in Chroma and Spectri, subsequent results report pooled data, with unpooled results in Supplement 3.

GA Enlargement by Clinical Subgroup

No consistent benefit of lampalizumab over sham was observed for any subgroup (eFigures 2-4 in Supplement 3).

Best-Corrected Visual Acuity

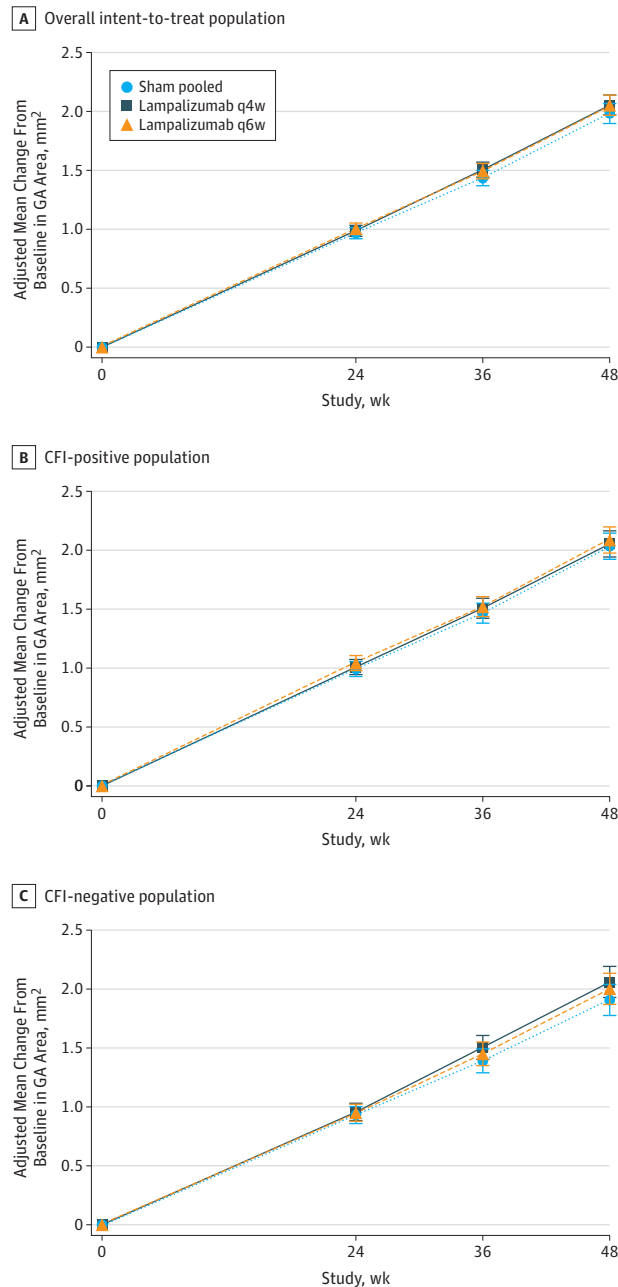
Best-corrected visual acuity declined from baseline to week 48 in all arms of both studies (eTable 9 and eFigure 5 in Supplement 3), with an adjusted mean BCVA letter score change of -4.9 (95% CI, -5.8 to -4.0) for sham treatment, -4.1 (95% CI, -5.0 to -3.2) for lampalizumab every 4 weeks, and -4.9 (95% CI, -5.8 to -3.9) for lampalizumab every 6 weeks.

Safety of Lampalizumab Treatment

No new ocular or nonocular safety signals beyond what would be anticipated with intravitreal injections were observed with lampalizumab through week 48 (eTables 10-19 in Supplement 3). The percentage of participants with ocular AEs and serious AEs (SAEs) were higher with lampalizumab compared with sham treatment, in alignment with expectations for intravitreal injections. Overall, 2.7% (17 of 619) of participants receiving the sham treatment, 6.2% (39 of 626) of participants receiving lampalizumab every 4 weeks, and 6.1% (38 of 626) of participants receiving lampalizumab every 6 weeks experienced 1 or more ocular SAEs.

Increases in intraocular pressure (IOP) were of interest because lampalizumab was injected as 0.1 mL, twice the volume of most intravitreal injections of anti-VEGF. Incidences of any IOP of 30 mm Hg or higher after injection, regardless of whether the events were considered SAEs, were reported in 0.3% (2 of 618) of participants receiving the sham treatment, 8.3% (52 of 625) of participants receiving lampalizumab every 4 weeks, and 5.6% (35 of 626) of participants receiving lampalizumab every 6 weeks. Increases in IOP considered to be SAEs were reported in 0.2% (1 of 619) of participants receiving the sham treatment, 3.2% (20 of 626) of the participants receiving lampalizumab every 4 weeks, and 2.6% (16 of 626) of participants receiving lampalizumab every 6 weeks. The mean preinjection IOP remained constant from baseline to

Figure 2. Adjusted Mean Change From Baseline in Geographic Atrophy (GA) Area Over Time From Baseline to 48 Weeks in Chroma and Spectri Pooled as Measured on Fundus Autofluorescence Imaging



A, Overall intent-to-treat population. B, Complement factor I (CFI)-positive population. C, CFI-negative population. The mixed effects model repeated-measures analysis was adjusted for baseline GA area, baseline GA lesion location, baseline GA lesion contiguity, baseline best-corrected visual acuity category, sex, biomarker status (overall population only), and study. Error bars indicate 95% CIs. q4w Indicates every 4 weeks; q6w, every 6 weeks.

week 48 across all arms (eTable 18 and eFigure 6 in Supplement 3). Per investigator discretion, 3.1% (39 of 1252) of participants receiving lampalizumab also received paracentesis in the study eye owing to AEs of increased IOP or transient vision loss (5.6 procedures per 1000 injections).

Endophthalmitis occurred after 5 of 12 447 injections (0.4 events per 1000 injections [0.04%]) or in 5 of 1252 treated participants (0.4%) through week 48. Neovascular AMD was observed after randomization in 1.1% (7 of 619) of study eyes in the group receiving the sham treatment, 1.9% (12 of 626) of study eyes in the group receiving lampalizumab every 4 weeks, 1.9% (12 of 626) of study eyes in the group receiving lampalizumab every 6 weeks, 1.3% (8 of 619) of fellow eyes in the group receiving the sham treatment, 1.6% (10 of 626) of fellow eyes in the group receiving lampalizumab every 4 weeks, and 1.8% (11 of 626) of fellow eyes in the group receiving lampalizumab every 6 weeks, with no events of bilateral neovascular AMD (eTable 19 in Supplement 3).

Nonocular SAEs were reported in 16.6% (103 of 619) of participants in the group receiving the sham treatment, including 7 deaths; 19.2% (120 of 626) of participants in the group receiving lampalizumab every 4 weeks, including 7 deaths; and 13.9% (87 of 626) of participants in the group receiving lampalizumab every 6 weeks, including 5 deaths.

Discussion

To our knowledge, Chroma and Spectri were the largest, most comprehensive studies of GA conducted to date. In the primary analysis, lampalizumab did not reduce the enlargement of GA lesions from baseline at week 48 vs sham. Furthermore, no benefit of lampalizumab was suggested by the results of robustness assessments or subgroup analyses, including by CFI-profile biomarker. No new safety signals were observed with lampalizumab treatment, and incidences of endophthalmitis, increase in IOP, or other injection-related SAEs were low and consistent with those observed in studies of anti-VEGF.^{5,6,33}

The Chroma and Spectri trials provide the largest cohorts to date of patients with bilateral GA and no CNV in either eye, with detailed documentation of anatomical and functional outcomes. The rates of progression of GA in Chroma and Spectri (approximately 2 mm² per year on average) were within the range of previous studies (approximately 0.53-2.6 mm² per year),¹⁵ with differences across studies likely attributable to inclusion criteria reflected in the characteristics of each study cohort. In Chroma and Spectri, eligibility criteria included factors associated with faster GA progression, such as bilateral GA and banded or diffuse perilesional fundus autofluorescence patterns.¹⁵ Consistent with prior studies,¹⁵ Chroma and Spectri subgroup analyses demonstrated that larger baseline GA lesion area, multifocal configurations, and nonfoveal GA lesions are associated with faster rates of progression. This large data set, from 2 multicenter global trials conducted in 23 countries, is likely generalizable to the broader population of patients with GA who would meet the eligibility criteria of these trials and could serve as an important normative database for future studies and provide further insights into the natural history of GA.

The Chroma and Spectri cohorts experienced a notable decline in visual function, with a mean BCVA letter score loss of approximately 5 letters in 48 weeks. This finding underscores the potential burden of vision loss from GA.

The safety outcomes presented here can inform future trials through at least 1 year. Intravitreal injection volumes of 0.1 mL were associated with low rates of increased posttreatment IOP SAEs and no change in mean pretreatment IOP during 48 weeks, suggesting that this volume may be given safely within a trial setting. Also, Chroma and Spectri documented that new CNV in patients with bilateral GA occurred in less than 2% of study or fellow eyes. This finding is consistent with observational studies, which reported conversion rates of 2% at 2 years and 11% at 4 years in patients with bilateral GA and no baseline CNV,³⁴ and a conversion rate of 1.5% by 1 to 2 years in studies in which most patients had bilateral GA.³⁵ In contrast, for patients with CNV in 1 eye and GA in the other, much higher rates of CNV in the eye with GA have been reported (18% at 2 years³⁴ and 34%-49% at 4-5 years^{34,36}), similar to conversion rates for eyes with large drusen or focal hyperpigmentations.^{36,37} Thus, future GA trials must consider the effect of including participants with any history of CNV in either eye because its presence may confound the accurate measurement of the enlargement of GA lesions and affect visual function assessments.

The primary rationales for exploring complement inhibition in GA were the strong genetic linkage and the feasibility of clinical trials evaluating the enlargement of GA lesions. To date, 6 molecules that act as complement pathway inhibitors have entered clinical trials for GA, including APL-2 (target, C3), which met its primary end point in a phase 2 trial³⁸; CLG-561 (target, properdin), currently in a phase 2 trial³⁹; and avacincaptad pegol (target, C5),⁴⁰ currently in a phase 2b trial. Two other C5 inhibitors, one given systemically⁴¹ and the other intravitreally,⁴² were not effective in phase 2 trials. Taken together with the Chroma and Spectri results, it remains unclear whether the complement cascade is an appropriate intraocular therapeutic target for GA, at least through the alternative pathway via complement factor D or downstream in the cascade via C5. Geographic atrophy therapeutics investigating targets outside the complement cascade are also in development.

Although the CFI-profile biomarker was thought to be associated with faster progression of GA based on the Mahalo phase

2 trial of lampalizumab,²⁹ the much larger prospective analysis of Chroma and of Spectri does not support CFI-profile status as a genetic biomarker for progression of GA. This finding is consistent with other studies performed after the initiation of Chroma and Spectri, which also reported no association between CFI risk alleles and the rate of GA progression.⁴³⁻⁴⁵ Although it is still not clear why such results were observed in Mahalo, in light of the results from Chroma and Spectri, one may hypothesize that they may have been related to a small sample size and may have occurred by chance.

Strengths and Limitations

There are several strengths and limitations of these studies that could affect the interpretation of the results. The randomization of a large cohort; duplication of results across 2 identically designed, multicenter, double-masked, randomized clinical trials; and good follow-up and adherence to the protocol make it less likely that confounding or bias affected these topline results. However, the results apply only to 48 weeks of treatment and may not apply to all cases of GA. Based on the inclusion and exclusion criteria of these trials, they may not apply to patients with smaller or larger lesions, unilateral GA, autofluorescence patterns other than banded or diffuse, eyes with current or prior CNV, GA from causes other than AMD, or earlier disease stages.

Conclusions

In 2 identically designed phase 3 trials, lampalizumab, a selective complement factor D inhibitor, did not reduce the enlargement of GA lesions vs sham. The results highlight both the potential burden of vision loss facing patients with bilateral GA and the substantial retinal tissue loss that occurs during 48 weeks. Further analysis of Chroma and Spectri, including genotype-phenotype correlations enabled by whole-genome sequencing, may yield additional insights into AMD pathophysiology and support future clinical trials.

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Author Affiliations: Department of Ophthalmology, University of Bonn, Bonn, Germany (Holz); Doheny Eye Institute, Los Angeles, California (Sadda); Department of Ophthalmology, University of California at Los Angeles (Sadda); Tennessee Retina, Nashville (Busbee); Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, Maryland (Chew); Department of Ophthalmology and Westmead Institute for Medical Research, University of Sydney, Sydney, Australia (Mitchell); Moorfields Eye Hospital, London, United Kingdom (Tufail); Genentech Inc, a Member of the Roche Group, South San Francisco, California (Brittain, Ferrara, Gray, Honigberg, Martin, Tong,

Ehrlich); Johns Hopkins University School of Medicine, Baltimore, Maryland (Bressler); Editor, *JAMA Ophthalmology* (Bressler).

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Study concept and design: Busbee, Chew, Mitchell, Brittain, Ferrara, Ehrlich, Bressler.

Acquisition, analysis, or interpretation of data: Holz, Sadda, Busbee, Chew, Tufail, Brittain, Ferrara, Gray, Honigberg, Martin, Tong, Ehrlich, Bressler.

Drafting of the manuscript: Busbee, Tufail, Brittain, Ferrara, Gray, Honigberg, Bressler.

Critical revision of the manuscript for important intellectual content: Holz, Sadda, Busbee, Chew, Mitchell, Brittain, Ferrara, Gray, Martin, Tong, Ehrlich, Bressler.

Statistical analysis: Gray, Martin, Tong.

Obtained funding: Ehrlich.

Administrative, technical, or material support: Brittain, Tong, Ehrlich.

Study supervision: Holz, Busbee, Mitchell, Brittain,

Ferrara, Tong, Ehrlich, Bressler.

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Group Information: The Chroma Study Investigators include Federico Furno Sola, Grupo Laser Vision, Rosario, Argentina; Patricio Schlottmann, Organizacion Medica De Investigacion, Capital Federal, Argentina; Alberto Zambrano, Fundacion Zambrano, Caba, Argentina; Carlos Zeolite, Oftar, Mendoza, Argentina; Jennifer Arnold, Marsden Eye Research Centre, Parramatta, Australia; Mark Gillies, Save Sight Institute, Sydney, Australia; Alan Luckie, Eyeclinic Albury Wodonga, Albury, Australia; Paul Mitchell, Sydney West Retina, Westmead, Australia; Nicole Schneltzer, Kepler Universitätsklinik Gmbh–Med Campus Iii; Abt Für Augenheilkunde, Linz, Austria; Julie De Zaeytijd, Uz Gent, Belgium; Shelley Boyd, St Michael's Hospital, Toronto, Canada; Alan Cruess, Qeii–Hsc Department of Ophthalmology, Halifax, Canada; Peter Kertes, Sunnybrook Health Sciences Centre, Toronto, Canada; Laurent Lalonde, Institut De L'oeil Des Laurentides, Boisbriand, Canada; David Maberley, University of British Columbia, Vancouver, Canada; Caroline Laugesen, Sjællands Universitetshospital, Roskilde; Øjenafdelingen, Roskilde, Denmark; Bahram Bodaghi, Ch Pitie Salpetriere; Ophtalmologie, Paris, France; Salomon Yves Cohen, Centre Ophtalmologique; Imagerie et Laser, Paris, France; Catherine Francais, Centre Odeon; Exploration Ophtalmologique, Paris, France; Eric Souied, Chi De Creteil; Ophtalmologie, Creteil, France; Ramin Tadayoni, Hopital Lariboisiere; Ophtalmologie, Paris, France; Lebriz Altay, Universitätsklinikum Köln; Augenklinik, Köln, Germany; Nicole Eter, Universitätsklinikum Münster; Augenheilkunde, Münster, Germany; Nicolas Feltgen, Universitätsmedizin Göttingen Georg-August-Universität; Klinik Für Augenheilkunde, Göttingen, Germany; Carsten Framme, Medizinische Hochschule Hannover, Klinik Für Augenheilkunde, Hannover, Germany; Salvatore Grisanti, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Klinik Für Augenheilkunde, Lübeck, Germany; Frank Holz, Universitäts-Augenklinik Bonn, Bonn, Germany; Daniel Pauleikhoff, Augenabteilung Am St

Franziskus-Hospital, Munster, Germany; András Seres, Budapest Retina Associates Kft., Budapest, Hungary; Attila Vajas, Debreceni Egyetem Klinikai Kozpont; Szemeszeti Klinika, Debrecen, Hungary; Balazs Varsanyi, Ganglion Medical Center, Pecs, Hungary; Francesco Boscia, Azienda Ospedaliero Universitaria Di Sassari; U. O. Oculistica, Sassari, Italy; Maria Cristina Parravano, Fondazione G. B. Bietti Per Lo Studio E. La Ricerca In Oftalmologia-Presidio Ospedaliero Britannico, Roma, Italy; Federico Ricci, Fondazione Ptv Policlinico Tor Vergata Di Roma; UOSD Patologie Renitiche, Roma, Italy; Francesco Viola, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico-Clinica Regina Elena; U. O. C. Oculistica, Milano, Italy; David Lozano Rechy, Macula Retina Consultores, Mexico, DF, Mexico; Virgilio Morales Canton, Hospital De La Ceguera Apec, Mexico, DF, Mexico; G. Dijkman, Leids Universitair Medisch Centrum, Leiden, Netherlands; Reinier Schlingemann, Academisch Medisch Centrum Universiteit Amsterdam, Amsterdam, Netherlands; Guillermo Reategui, Clinica Anglo Americana, Lima, Peru; Dorota Raczyska, Optimum Proforskie Centrum Okulistyki, Gdańsk, Poland; Bożena Romanowska-Dixon, Sp Zoz Szpital Uniwersytecki W Krakowie Oddział Kliniczny Okulistyki I Onkologii Okulistycznej, Krakow, Poland; Sławomir Teper, Gabinet Okulistyczny Prof Edward Wylegala, Katowice, Poland; Marek Kacerik, Fakultna Nemocnica Trencin Ocna Klinika, Trencin, Slovakia; Blandina Lipkova, Fakultna Nemocnica S Poliklinikou Zilina; Ocne Oddelenie, Zilina, Slovakia; Hedviga Mikova, Nemocnica Sv. Michala, AS, Bratislava, Slovakia; Javier Araiz, Instituto Clinico Quirurgico De Oftalmologia-Icqo, Bilbao, Spain; Luis Arias, Hospital Universitario De Bellvitge; Servicio De Oftalmologia, Hospital De Llobregat, Spain; Jorge Mataix, Fisabio. Fundación Oftalmologica Del Mediterraneo, Valencia, Spain; Jordi Mones, Institut De La Macula I La Retina, Barcelona, Spain; Javier Montero, Hospital Universitario Rio Hortega; Servicio De Oftalmologia, Valladolid, Spain; Laura Sararols, Hospital General De Catalunya, Sant Cugat Del Vallès, Spain; Stephan Michels, Stadtsptal Triemli; Augenklinik, Zürich, Switzerland; Christopher Brand, Royal Hallamshire Hospital, Sheffield, UK; Baljean Dhillon, The Princess Alexandra Eye Pavilion, Edinburgh, UK; Anita Agarwal, Vanderbilt University, Nashville, Tennessee; Virgil Alfaro, Charleston Neuroscience Institute, Ladson, South Carolina; Brad Baker, Vitreo-Retinal Associates, PC, Worcester, Massachusetts; Brian Berger, Retina Research Center, Austin, Texas; Robert Bhisitkul, Ophthalmology, University of California San Francisco; Barbara Blodi, University of Wisconsin, Madison; David Boyer, Retina-Vitreous Associates Medical Group, Beverly Hills, California; H. Logan Brooks Jr, Southern Vitreoretinal Associates, Tallahassee, Florida; Stuart Burgess, Fort Lauderdale Eye Institute, Plantation, Florida; Brandon Busbee, Tennessee Retina PC, Nashville; Miguel Busquets, Associates in Ophthalmology, West Mifflin, Pennsylvania; David Callanan, Texas Retina Associates, Arlington; Clement Chan, Southern California Desert Retina Consultants, Palm Desert; Jeffrey Chang, Lahey Clinic Medical Center, Peabody, Massachusetts; Sanford Chen, Orange County Retina Medical Group, Santa Ana, California; James Combs, Eye Surgeons of Richmond Inc, Dba Virginia Eye Institute, Richmond; Dilsher Dhoot, California Retina

Consultants, Bakersfield; Pravin Dugel, Retinal Research Institute LLC, Phoenix, Arizona; David Eichenbaum, Retina Vitreous Associates of Florida, Saint Petersburg; Richard Feist, University of Alabama at Birmingham Clinical Research Unit; Philip Ferrone, Long Island Vitreoretinal Consult, Great Neck, New York; Howard Fine, New Jersey Retina Research Foundation, Toms River; Jorge Fortun, Bascom Palmer Eye Institute, Palm Beach Gardens, Florida; Gregory A. Fox, Retina Associates, Shawnee Mission, Kansas; Arthur Fu, West Coast Retina Medical Group Inc, San Francisco, California; Ronald Gentile, New York Eye & Ear Infirmary, New York, New York; Ghassan Ghorayeb, West Virginia University Eye Institute, Morgantown; Manjot Gill, Northwestern Medical Group/Northeastern University, Chicago, Illinois; Victor Gonzalez, Valley Retina Institute PA, McAllen, Texas; Carmelina Gordon, Specialty Eye Institute, Jackson, Mississippi; Sunil Gupta, Retina Specialty Institute, Pensacola, Florida; Robert Hampton, Retina Vitreous Surgeons of Central New York, Syracuse; Jeffrey Heier, Ophthalmic Consultants of Boston, Boston, Massachusetts; Vrinda Hershberger, Florida Eye Associates, Melbourne; Patrick Higgins, Retina Center of New Jersey, Bloomfield; Darma Ie, Delaware Valley Retina Associates, Lawrenceville, New Jersey; Ricky Isernhagen, Retina Associates of Kentucky, Lexington; Randy Katz, Florida Eye Microsurgical Institute, Boynton Beach; Gregg Kokame, Retina Consultants of Hawaii, Aiea; Robert Kwun, Retina Associates of Utah, Salt Lake City; Paul Lee, Retina Consultants of Western New York, Orchard Park; Seong Lee, Strategic Clinical Research Group LLC, Willow Park, Texas; Sam Mansour, Virginia Retina Centers, Warren; Dennis Marcus, Southeast Retina Center, Augusta, Georgia; Raj Maturi, Midwest Eye Institute Northside, Indianapolis, Indiana; Mark Michels, Retina Care Specialists, Palm Beach Gardens, Florida; Jeffrey Moore, Maine Eye Center, Portland; Jared Nielsen, Wolfe Eye Clinic, West Des Moines, Iowa; George Novalis, Retina Centers PC, Tucson, Arizona; Michael Ober, Retina Consultants of Michigan, Southfield; Karl Olsen, Retina Vitreous Consultants, Monroeville, Pennsylvania; Sunil Patel, Retina Research Institute of Texas, Abilene; Dante Pieramici, California Retina Consultants, Santa Barbara; Paul Raskauskas, National Ophthalmic Research Institute, Fort Myers, Florida; Soraya Rofagha, East Bay Retina Consultants, Oakland, California; Alan Ruby, Associated Retinal Consultants PC, Royal Oak, Michigan; Todd Schneiderman, Retina Center Northwest, Silverdale, Washington; Steven Schwartz, Jules Stein Eye Institute/University of California Los Angeles; Rajiv Shah, Wake Forest Baptist Health Eye Centre, Winston-Salem, North Carolina; Veeral Sheth, University Retina and Macula Associates PC, Oak Forest, Illinois; Lawrence Singerman, Retina Associates of Cleveland Inc, Beachwood, Ohio; Rishi Singh, Cleveland Clinic Foundation and Cole Eye Institute, Cleveland, Ohio; Raymond Sjaarda, Retina Specialists, Towson, Maryland; Glenn Stoller, Ophthalmic Consultants of Long Island, Lynbrook, New York; Robert Stoltz, Georgia Retina PC, Marietta; Ivan Suner, Retina Associates of Florida LLC, Tampa; Ali Tabassian, Retina Institute of Virginia, Richmond; Ryan Tarantola, Retina Specialty Institute, Pensacola, Florida; Allen Thach, Retina Consultants of Nevada, Henderson; Rafael Ufret-Vincenty, University of Texas Southwestern Medical Center at Dallas; Robert Wirthlin, Spokane

Eye Clinical Research, Spokane, Washington; Andre Witkin, Tufts Medical Center Research, Boston, Massachusetts; Robert Wong, Austin Retina Associates, Austin, Texas; Matthew Wood, Eye Surgical Associates, Lincoln, Nebraska; and Jeffrey Zheutlin, Vitreo-Retinal Associates, Grand Rapids, Michigan.

The Spectri Study Investigators include Arturo Alezzandrini, Oftalmos, Capital Federal, Argentina; Mauricio Martinez Cartier, Instituto De La Vision, Capital Federal, Argentina; Devinder Chauhan, Vision Eye Institute Eastern, Box Hill, Australia; Fred Chen, The Lions Eye Institute, Nedlands, Australia; Jagjit Gilhotra, Adelaide Eye and Retina Centre, Adelaide, Australia; Robyn Guymer, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia; Anthony Kwan, Queensland Eye Institute, Brisbane, Australia; Ursula Schmidt-Erfurth, Medizinische Universität Wien; Universitätsklinik für Augenheilkunde und Optometrie, Vienna, Austria; Julie Jacob, Uz Leuven Sint Rafael, Leuven, Belgium; Laurence Postelmans, Chu Brugmann (Victor Horta), Brussels, Belgium; Michael Larsen, Glostrup Hospital, Øjenafdelingen, Forskningsafsnit Ø37, Glostrup, Denmark; Catherine Creuzot Garcher, Chu Bocage; Ophtalmologie, Dijon, France; Francois Devin, Centre Paradis Monticelli; Ophtalmologie, Marseille, France; Laurent Kodjikian, Hôpital De La Croix Rousse; Ophtalmologie, Lyon Cedex, France; Jean Francois Korobelnik, Hôpital Pellegrin; Ophtalmologie, Bordeaux, France; Saddek Mohand Said, CHNO des Quinze Vingts; Ophtalmologie, Paris, France; Michel Weber, Hôpital Hotel Dieu Et Hme; Clinique Ophtalmologique, Nantes, France; Hansjürgen Agostini, Universitätsklinikum Freiburg, Klinik Für Augenheilkunde, Freiburg, Germany; Gerd Auffarth, Universitätsklinik Heidelberg; Augenklinik, Heidelberg, Germany; Ulrich Bartz-Schmidt, Universitätsklinikum Tübingen, Tübingen, Germany; Katharina Bell, Universitätsmedizin Der Johannes Gutenberg-Universität Mainz, Augenklinik Und Poliklinik, Mainz, Germany; Andreea Gamulescu, Universitätsklinikum Regensburg, Klinik & Poliklinik Für Augenheilkunde, Regensburg, Germany; Lars-Olof Hattenbach, Klinikum Der Stadt Ludwigshafen Am Rhein Ggmbh; Augenklinik, Ludwigshafen, Germany; Chris P. Lohmann, Klinikum Rechts der Isar der Tu München; Augenklinik, München, Germany; Armin Wolf, Lmu Klinikum der Universität, Augenklinik, München, Germany; Janos Nemeth, Semmelweis Egyetem Aok, Szemeszeti Klinika, Budapest, Hungary; Péter Vámosi, Peterfy Sandor Utcai Korhaz-Rendelőintézet Es Baleseti Kózpont, Szemeszet Kr, Budapest, Hungary; Balazs Varsanyi, Ganglion Medical Center, Pecs, Hungary; Francesco Bandello, IRCCS Ospedale San Raffaele; U. O. Oculistica, Milano, Italy; Chiara Eandi, ASL To1 Presidio Ospedaliero Sperino Oftalmico, Torino, Italy; Paolo Lanzetta, AO Universitaria S. Maria Della Misericordia Di Udine; Clinica Oculistica, Udine, Italy; Massimo Nicolo, Università Degli Studi Di Genova-DiNOG; Clinica Oculistica, Genova, Italy; Giovanni Staurenghi, Asst Fatebenefratelli Sacco; Oculistica (Sacco), Milano, Italy; Gianni Virgili, Azienda Ospedaliero-Universitaria Careggi; SOD Oculistica, Firenze, Italy; Renata Garcia Franco, Instituto Mexicano De Oftalmologia I.A.P., Querétaro, Mexico; Juan Ramirez Estudillo, Hospital Nuestra Señora De La Luz, Mexico City, Mexico; Carel Hoyng, Radboud University Nijmegen Medical Centre; Ophthalmology, Nijmegen, Netherlands;

Carlos Fernandez, Centro De Investigacion Oftalmolaser, Lima, Peru; Miguel Guzman, Tg Laser Oftalmica, Lima, Peru; Silvio Lujan, Mácula D&T, Lima, Peru; Ewa Herba, Szpital Specjalistyczny Nr 1; Oddzial Okulistyczny, Bytom, Poland; Jozef Kaluzny, Oftalmika Sp Z. O. O., Bydgoszcz, Poland; Marta Misiuk-Hojło, Uniwersytecki Szpital Kliniczny; Klinika Okulistyki, Wrocław, Poland; Jerzy Nawrocki, Klinika Okulistyczna Jasne Błonia, Łódź, Poland; Angela Carneiro, Hospital De Sao Joao; Servico De Oftalmologia, Porto, Portugal; Joao Figueira, Espaço Medico Coimbra, Coimbra, Portugal; Rufino Silva, Aibili-Association for Innovation and Biomedical Research On Light, Coimbra, Portugal; Sara Vaz-Pereira, Hospital De Santa Maria; Servico De Oftalmologia, Lisboa, Portugal; Elmira Abdulaeva, Sahi "Republic Clinical Ophthalmological Hospital of Ministry of Heal of Tatarstan Republic", Kazan, Russian Federation; Valery Erichev, Fsb "Scientific Research Institute of Eye Diseases" of Russian Academy of Medical Sciences, Moscow, Russian Federation; Andrey Zolotarev, St Educ Inst of High Prof Education "Samara State Medical University"; Chair of Ophthalmology, Samara, Russian Federation; Andrej Cernak, Univerzitna Nemocnica Bratislava, Nemocnica Sv Cyrila A. Metoda Ocna Klinika Szu a Unb, Bratislava, Slovakia; Marta Figueroa, Visum Madrid Santa Hortensia, Madrid, Spain; Roberto Gallego-Pinazo, Hospital Universitario La Fe; Servico De Oftalmologia, Valencia, Spain; Alfredo Garcia-Layana, Clinica Universitaria De Navarra; Servico De Oftalmologia, Pamplona, Spain; Francisco Gomez Ulla, Instituto Oftalmologico Gomez Ulla, Santiago De Compostela, Spain; Rafael Navarro, Instituto De Microcirugia Ocular, Barcelona, Spain; Jose Manuel Ortiz, Hospital Perpetuo Socorro; Servico De Oftalmologia, Albacete, Spain; Ramon Torres Imaz, Hospital Universitario Clinico San Carlos; Servico De Oftalmologia, Madrid, Spain; Anders Kvanta, St Eriks Eye Hospital, Stockholm, Sweden; Katja Hatz, Vista Klinik Binningen, Binningen, Switzerland; Sebastian Wolf, Inselspital Bern, Universitätsklinik Für Augenheilkunde, Bern, Switzerland; Bora Eldem, Hacettepe University Medical Faculty; Department of Ophthalmology, Ankara, Turkey; Nur Kir, Istanbul University Istanbul Medical Faculty; Department of Ophthalmology, Istanbul, Turkey; Jale Mentess, Ege University Medical Faculty; Department of Ophthalmology, Izmir, Turkey; Osman Saatci, Dokuz Eylul University Medical Faculty; Department of Ophthalmology, Izmir, Turkey; Gursel Yilmaz, Ankara Baskent University Medical Faculty; Department of Ophthalmology, Ankara, Turkey; Clare Bailey, Bristol Eye Hospital, Bristol, UK; Sanjiv Banerjee, University Hospital of Wales, Cardiff, UK; Andrew Browning, Royal Victoria Infirmary, Newcastle Upon Tyne, UK; Simona Esposito, Moorfields Eye Hospital NHS Foundation Trust, London, UK; Richard Gale, The York Hospital, York, UK; Faruque Ghanchi, Bradford Royal Infirmary, Bradford, UK; Tim Jackson, Kings College Hospital, London, UK; Andrew Lotery, Southampton General Hospital, Southampton, UK; Sajjad Mahmood, Macular Treatment Centre; Royal Eye Hospital, Manchester, UK; Quresh Mohamed, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK; Niro Narendran, The Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK; Ian Pearce, Royal Liverpool University Hospital; St Paul's Clinical Eye Research Centre, Liverpool, UK; Michael Williams, Royal

Victoria Hospital, Belfast, UK; Prema Abraham, Black Hills Regional Eye Institute, Rapid City, South Dakota; Gary Abrams, Kresge Eye Institute, Detroit, Michigan; Sean Adrean, Retina Consultants of Orange County, Fullerton, California; Virgil Alfaro, Charleston Neuroscience Institute, Ladson, South Carolina; Andrew Antoszyk, Charlotte Eye Ear Nose & Throat Associates, Charlotte, North Carolina; Carl Baker, Paducah Retinal Center, Paducah, Kentucky; Richard Breazeale, Southeastern Retina Associates Chattanooga, Chattanooga, Tennessee; William Z. Bridges Jr, West Carolina Retinal Associates PA, Asheville, North Carolina; H. Logan Brooks Jr, Southern Vitreoretinal Associates, Tallahassee, Florida; David M. Brown, Retina Consultants of Houston, Houston, Texas; Jorge Calzada, Charles Retina Institute, Germantown, Tennessee; Peter Campochiaro, Wilmer Eye Institute, Baltimore, Maryland; Nauman Chaudhry, Retina Group of New England, New London, Connecticut; Lloyd Clark, Palmetto Retina Center, West Columbia, South Carolina; Brian Connolly, Retina Assoc of Western New York, Rochester; Karl Csaky, Texas Retina Associates, Dallas; Diana Do, University of Nebraska Medical Center Truhlsen Eye Institute, Omaha; Richard Dreyer, Retina Northwest, Portland, Oregon; William Durant, Sierra Eye Associates, Reno, Nevada; Alexander Eaton, Retina Health Center, Ft Myers, Florida; David Eichenbaum, Retina Vitreous Associates of Florida, St Petersburg; Leonard Feiner, Retina Associates of New Jersey, Teaneck; Henry Ferreyra, University of California San Diego Shiley Eye Center, La Jolla; Christina Flaxel, Oregon Health and Science University and Casey Eye Institute, Portland; Scott Foxman, Retinal & Ophthalmic Consultants PC, Northfield, New Jersey; K. Bailey Freund, Vitreous-Retina-Macula, New York, New York; Christine R. Gonzales, Retina & Vitreous Center of Southern Oregon, Ashland; Alan Gordon, Associated Retina Consultants, Phoenix, Arizona; Larry Halperin, Retina Group of Florida, Ft Lauderdale; Allen Ho, Mid-Atlantic Retina, Huntingdon Valley, Pennsylvania; Nancy Holekamp, Pepose Vision Institute, Chesterfield, Missouri; Deeba Husain, Massachusetts Eye and Ear Infirmary, Boston; Nieraj Jain, Emory University, Atlanta, Georgia; Cameron Javid, Retina Associates Southwest PC, Tucson, Arizona; Mark Johnson, University of Michigan, Kellogg Eye Center, Ann Arbor; Mark Johnson, Retina Group of Washington, Chevy Chase, Maryland; Szilard Kiss, New York Weil Cornell Medical Center, New York, New York; Eleonora Lad, Duke University Eye Center, Vitreoretinal, Durham, North Carolina; Theodore Leng, Byers Eye Institute at Stanford, Palo Alto, California; Mimi Liu, Colorado Retina Associates PC, Golden; Nikolas London, Retina Consultants, San Diego, California; Brian Madow, University of South Florida, Tampa; Daniel Miller, Cincinnati Eye Institute, Cincinnati, Ohio; Lawrence Morse, University of California, Davis, Eye Center, Sacramento; Jared Nielsen, Wolfe Eye Clinic, West Des Moines, Iowa; Matthew Ohr, Ohio State University Eye Physicians & Surgeons, Columbus; Scott Oliver, University of Colorado, Aurora; Sunil Patel, Retina Research Institute of Texas, Abilene; Joel Pearlman, Retinal Consultants Medical Group, Sacramento, California; Dante Pieramici, California Retina Consultants, Santa Barbara; Subhransu K. Ray, Bay Area Retina Associates, Walnut Creek, California; Carl Regillo, Mid Atlantic Retina, Philadelphia, Pennsylvania; Robert Rosa, Scott and White Hospital, Temple, Texas; Philip Rosenfeld,

Bascom Palmer Eye Institute, Miami, Florida; David Saperstein, Vitreoretinal Associates of Washington, Bellevue; David Sarraf, Jules Stein Eye Institute/University of California Los Angeles; Yevgeniy Shildkrot, University of Virginia Ophthalmology, Charlottesville; Raymond Sjaarda, Retina Specialists, Towson, Maryland; Eric Suan, The Retina Care Center, Baltimore, Maryland; Paul Weishaar, Vitreo Retinal Consultants, Wichita, Kansas; Mark Wieland, Northern California Retina Vitreous Associates, Mountain View; David Williams, Vitreoretinal Surgery, Edina, Minnesota; Jonathan Williams, Retina Consultants of Southern Colorado, Colorado Springs; and Charles C. Wykoff, Retina Consultants of Houston, The Woodlands, Texas.

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