

Intraocular Pressure Outcomes After Lampalizumab Injections in Patients With Geographic Atrophy

Neil M. Bressler, MD; K. Bailey Freund, MD; Sophie J. Bakri, MD; Judy E. Kim, MD; Daniela Ferrara, MD, PhD; Christopher Brittain, MBBS; Karen Pickthorn, DVM, MS; Hugh Lin, MD; Christy Sun, MS; Jillian Martin, MD, MPH

 Supplemental content

IMPORTANCE Intraocular pressure (IOP) elevations of clinical relevance have been observed after the commonly used 0.05-mL volume for intravitreal injections. However, more recently approved intravitreal agents involve volumes from 0.07 to 0.1 mL. It is not well established whether repeated 0.1-mL intravitreal injections may result in IOP-related complications.

OBJECTIVE To investigate the effect of 1 year of repeated 0.1-mL intravitreal injections on IOP outcomes.

DESIGN, SETTING, AND PARTICIPANTS This study was a post hoc analysis of 2 clinical trials investigating the IOP safety of intravitreal lampalizumab on geographic atrophy secondary to age-related macular degeneration. Both trials were conducted between 2014 and 2018 and recruited participants who were 50 years or older and had bilateral geographic atrophy. This post hoc analysis was performed between 2018 and 2022.

INTERVENTIONS Intravitreal lampalizumab, 0.1 mL, every 4 weeks; lampalizumab, 0.1 mL, every 6 weeks; or sham procedure every 4 weeks or 6 weeks for 48 weeks.

MAIN OUTCOMES AND MEASURES IOP changes in the 4-week-frequency study arms and ocular adverse events to week 48 in all arms. The hypothesis for this analysis was formulated after data collection.

RESULTS Among a total of 1851 participants, there was no change in mean pre-injection IOP values through 48 weeks in either arm. The adverse events glaucoma and ocular hypertension were reported for 1.8% of participants treated with lampalizumab and 1.6% of those in the sham arm.

CONCLUSIONS AND RELEVANCE Over 1 year, IOP increases were rare and did not affect treated participants more frequently than sham arm participants. These findings support the low risk of persistent IOP increases, on average, of intravitreal 0.1-mL injection volumes administered for 1 year in a manner similar to that performed in these clinical trials. These results may be valuable in the design of future therapeutic trials considering this volume for injections particularly as more recently approved agents use volumes of 0.07 to 0.1 mL.

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Author Affiliations: Johns Hopkins University School of Medicine, Baltimore, Maryland (Bressler); Vitreous Retina Macula Consultants of New York, New York (Freund); Department of Ophthalmology, New York University Grossman School of Medicine, New York (Freund); Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota (Bakri); Department of Ophthalmology and Visual Sciences, Medical College of Wisconsin, Milwaukee (Kim); Genentech, South San Francisco, California (Ferrara, Brittain, Pickthorn, Lin, Sun, Martin); Editor, JAMA Ophthalmology (Bressler).

Corresponding Author: Jillian Martin, MD, MPH, Genentech, One DNA Way, South San Francisco, CA 94080 (martin.jillian@gene.com).

Age-related macular degeneration (AMD) is a leading cause of blindness in the US.¹ The first line of clinical practice management for symptomatic neovascular AMD is frequent intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF).^{2,3} Although anti-VEGF agents are approved by the US Food and Drug Administration approved and associated with low incidence of serious adverse events (AEs),⁴ acute increases in intraocular pressure (IOP) were reported in patients receiving 0.05-mL intravitreal anti-VEGF injections.⁵ Typically, IOP returns to baseline at 30 minutes or less postinjection⁵; however, chronic increases in IOP have been reported in a small proportion of patients.^{6,7} Recently approved intravitreal agents have involved greater monthly or every other month volumes of 0.07 to 0.1 mL.⁸⁻¹⁰

Lampalizumab is an antigen-binding fragment of a humanized monoclonal antibody that inhibits complement factor D.^{11,12} It was evaluated in participants with geographic atrophy, an advanced stage of AMD, in 2 identical phase 3 clinical trials, CHROMA and SPECTRI.¹² Trial participants received repeated doses of intravitreal lampalizumab, 0.1 mL, twice the volume used for anti-VEGF intravitreal injections in clinical practice, allowing study of the effects of repeated intravitreal injections larger than 0.05 mL. The current study investigated IOP outcomes at 1 year, including glaucoma and ocular hypertension, after 1 year of repeated injections of 0.1-mL volume.

Methods

Trial Design and Participants

The CHROMA (NCT02247479) and SPECTRI (NCT02247531) studies were identical global, randomized, double-masked, sham injection-controlled, phase 3 trials in geographic atrophy.¹² Participants were randomized in a 2:1:2:1 ratio to receive intravitreal lampalizumab, 10 mg/0.1 mL, every 4 weeks; sham procedure every 4 weeks; lampalizumab, 10 mg/0.1 mL, every 6 weeks; or sham procedure every 6 weeks, respectively.¹²

Current analyses address the data for the 4-week-frequency arms, assuming that monthly treatments potentially carry higher risk for IOP-related AEs. IOP data analyses from 6-week-frequency arms are reported in the eAppendix in Supplement 1, along with additional details on inclusion and exclusion criteria and the lampalizumab injection procedure. Note that the current study did not require ethical review because it reports post hoc analyses of data from 2 clinical trials and is not the primary publication from either trial.

IOP Measurement

IOP was measured at screening, at baseline, and before treatment administration at every study visit in both the study and fellow eyes. The measurement method was chosen by the site investigator and remained consistent for each participant throughout the study. For approximately 100 of 1881 enrolled participants, optional aqueous humor sampling occurred on day 1 and at weeks 24 and 44 before the start of ocular

Key Points

Question What are the intraocular pressure (IOP)-related outcomes associated with repeated 0.1-mL intravitreal injections for 1 year?

Findings This post hoc analysis of data from 2 randomized clinical trials found low rates of clinically relevant IOP-related events after 1 year of intravitreal injections of lampalizumab, 0.1 mL.

Meaning These results suggest that repeated 0.1-mL intravitreal injections can be administered with a low risk of IOP-related adverse events, which is valuable in designing future therapeutic trials of intravitreal agents that use volumes of 0.07 to 0.1 mL.

assessments or study treatment. A finger counting test was conducted 15 minutes or sooner after treatment administration, followed by IOP measurement only in the study eye at 30 and 50 minutes after study treatment administration. If IOP increased 10 mm Hg or more, it was measured again 60 to 80 minutes posttreatment. Data points both before and after the injection were not censored for participants who had aqueous humor collection performed because of a small participant population.

Definitions for IOP Elevation and AEs

Increased IOP was defined by several established criteria (eTable 1 in Supplement 1).^{6,13,14} AEs indicative of persistent IOP changes were assessed, including incident and worsening of ocular hypertension and glaucoma, as diagnosed by the investigator. The eAppendix in Supplement 1 provides details on the management of IOP-related ocular AEs.

Results

Treatment Overview

Baseline ocular characteristics for the every-4-weeks groups are summarized in the Table. The mean (SD) numbers of injections per participant in lampalizumab (n = 627) and sham procedure (n = 311) arms were 11.6 (2.7) and 11.7 (2.7), respectively.

IOP Changes

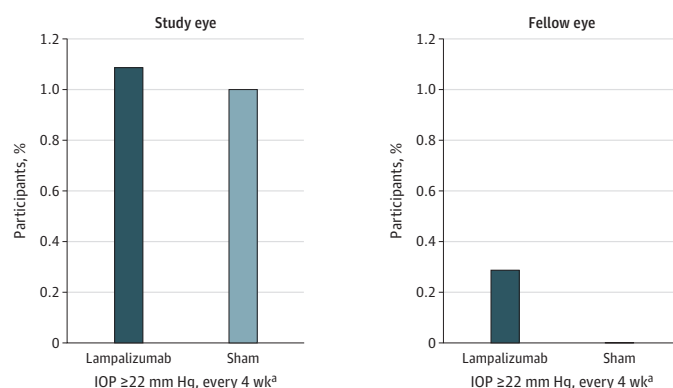
There was no change in mean pre-injection IOP values through 48 weeks in both 4-week-frequency arms (eFigure 1 in Supplement 1). Most study eyes (lampalizumab every 4 weeks, 85.7%; sham every 4 weeks, 91.6%) had maximum postbaseline preprocedural IOPs of 21 mm Hg or less (eFigure 2 in Supplement 1). The every-6-weeks arm results did not appear to be different from the 4-week-frequency arms and are reported in eFigures 3 and 4 in Supplement 1.

Three established criteria for defining sustained IOP elevation were applied in the current analysis (eTable 1 in Supplement 1). Applying DRCR.net criteria¹³ showed that the majority of changes from baseline preprocedural IOP were less than 6 mm Hg (Figure 1). Applying criteria by Bakri et al⁶ showed that a higher proportion of study eyes in the 4-week-frequency lampalizumab arm compared with those in the sham arm had maximum preprocedural IOP measurements of at least 21, 25, or 30 mm Hg with

Table. Ocular Characteristics at Baseline for Participants in the Study Arms Receiving Injections Every 4 Weeks

	Study eye, No. (%)		Fellow eye, No. (%)	
	Lampalizumab, 10 mg, every 4 wk (n = 628)	Sham every 4 wk (n = 314)	Lampalizumab, 10 mg, every 4 wk (n = 628)	Sham every 4 wk (n = 314)
Lens status				
Phakic	241 (38.4)	121 (38.5)	237 (37.7)	121 (38.5)
Pseudophakic	385 (61.3)	192 (61.1)	389 (61.9)	192 (61.1)
Other	2 (0.3)	1 (0.3)	2 (0.3)	1 (0.3)
Medical history				
Overall ^a	56 (8.9)	19 (6.1)	65 (10.4)	22 (7.0)
Glaucoma	42 (6.7)	15 (4.8)	49 (7.8)	18 (5.7)
Glaucoma (suspect)	10 (1.6)	3 (1.0)	9 (1.4)	3 (1.0)
Ocular hypertension	5 (0.8)	1 (0.3)	7 (1.1)	1 (0.3)

^a Overall refers to a history of glaucoma, glaucoma (suspect), or ocular hypertension.

Figure 1. Application of DCRC.net Criteria for Intraocular Pressure (IOP) Elevation¹³

^aA ≥ 6 mm Hg increase from baseline and occurring on ≥ 2 consecutive visits at least 1 month apart.

changes of at least 6, 8, or 10 mm Hg from baseline preprocedural IOP (Figure 2A and B). These trends were also seen in fellow eye results. IOP changes per criteria by Morshedi et al¹⁴ showed a slight sustained increase in IOP of at least 21 mm Hg in the sham arm (1.8%) greater than the 4-week-frequency treatment arm (1.3%) (eFigure 5 in Supplement 1).

Overview of IOP AEs

The AEs of glaucoma and ocular hypertension as well as other serious ocular AEs related to IOP are summarized in eTables 3 and 4 in Supplement 1, respectively. Events requiring IOP-lowering medication were reported more in the lampalizumab arm than the sham arm (65/ 628 participants [10.4%] vs 5/314 [1.6%]) (eTable 2 in Supplement 1). However, most participants who required IOP-lowering medications or procedures to treat these AEs only required these interventions for a single day (lampalizumab: 41/65 [63.1%]; sham procedure arm: 3/5 [60.0%]) (eTable 2 in Supplement 1).

Discussion

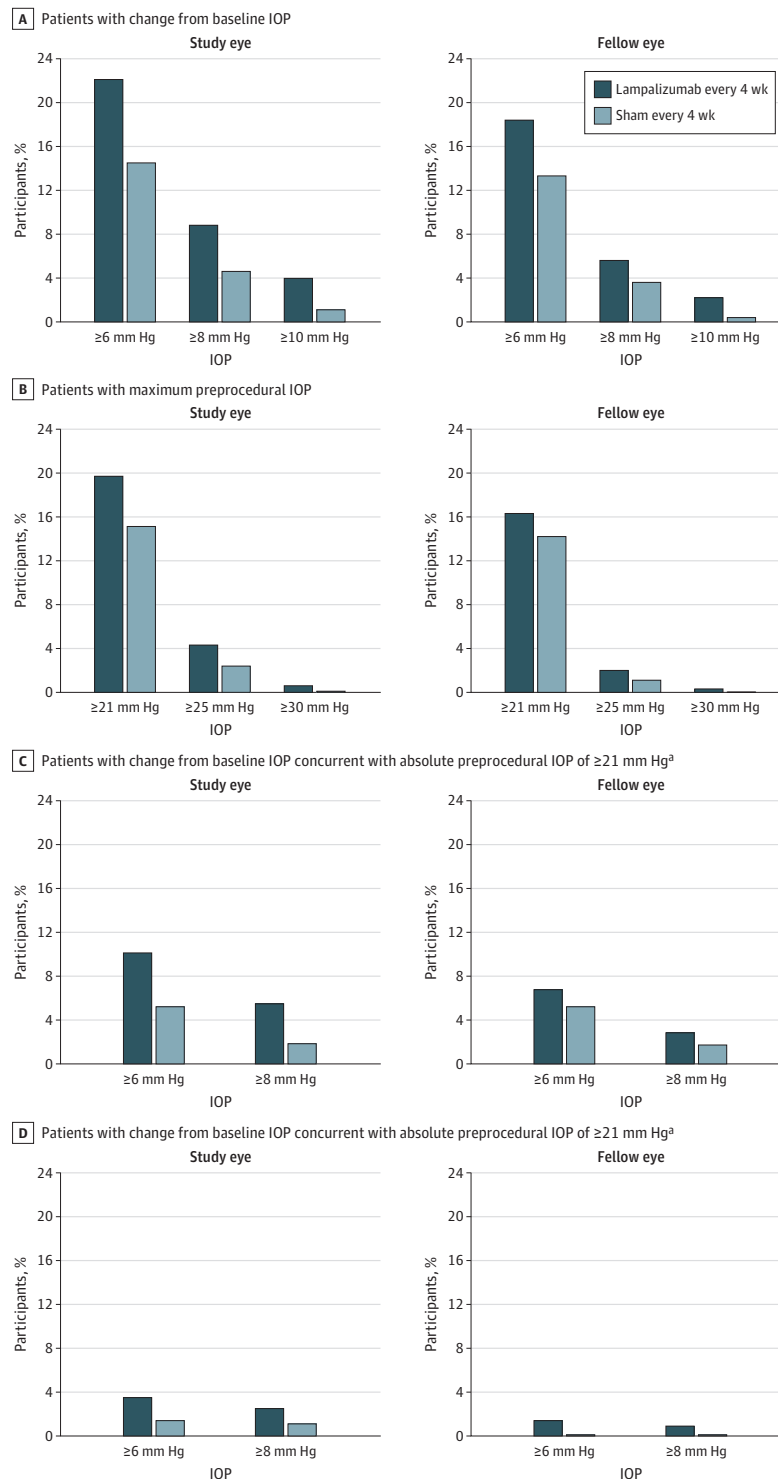
Most participants in the lampalizumab and sham arms experienced mild posttreatment IOP increases of less than 10 mm Hg. One-time elevations of at least 6 or 8 mm Hg occurred slightly

more frequently in the lampalizumab-treated group in participants with an absolute or discrete preprocedural IOP measurement of 21 mm Hg or greater as compared with their baseline value (Figure 2). IOP increases based on Bakri et al⁶ criteria occurred slightly more often in participants treated with lampalizumab compared with sham in both study and fellow eyes. Glaucoma and ocular hypertension events were low in both arms. In addition, most participants did not require IOP-lowering medications, and most interventions lasted a single day.

Strengths and Limitations

The study strengths include using clinical trial data, a sham procedure-controlled arm, and a large sample size. Data analysis was based on previously established criteria for IOP increase,^{6,13,14} facilitating future potential comparisons.

This analysis has several limitations. Method of measuring IOP were not protocol-specified. Ocular axial length was not measured, and scleral rigidity was not evaluated, which may have affected clinical interpretation of IOP changes. No placebo injection was used, which might have allowed for evaluation of any IOP effect related to lampalizumab independent of the volume of vehicle injected. While unlikely, pressure from the sham treatment might have had an effect on IOP compared with no treatment. Glaucoma rates were based on site

Figure 2. Application of Intraocular Pressure (IOP) Elevation Criteria Defined by Bakri et al⁶

^aAbsolute preprocedural IOP refers to a discrete measurement of preprocedural IOP during the 48 weeks that differed from the IOP at baseline.

investigator diagnoses and reported AEs but not confirmed by a glaucoma specialist. Participants with advanced glaucoma were excluded from the trials; therefore, extrapolation of these analysis results should not be extended to such participants. Investigators may have been less likely to enroll participants with a less severe degree of glaucoma because of a perceived potential effect on IOP. In addition, approximately 100 of 1881 enrolled participants had aqueous humor samples taken (~100 μ L) before the study procedure. These participants may have had lower IOP measurements prior to study treatment administration, which could disguise IOP elevations after treatment administration. Findings stem from a post hoc analysis, which provides hypotheses for future investigations but cannot determine or rule out a definitive causal relationship between these

injections and IOP changes. However, from this analysis, over the 48-week follow-up period, no persistent increase in mean preinjection IOP was observed.

Conclusions

Findings suggest that a volume of 0.1 mL, at least within the formulation of lampalizumab, can be administered by intravitreal injection monthly over 1 year with low risk of persistent ocular IOP alterations. This information could help inform future clinical trial design as well as support safety evaluations of more recently approved intravitreal injections that use volumes of 0.07 to 0.1 mL.

ARTICLE INFORMATION

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Concept and design: Bressler, Freund, Bakri, Kim, Ferrara, Brittain, Pickthorn, Martin.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Freund, Kim, Ferrara, Brittain, Martin.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Sun.

Obtained funding: Martin.

Administrative, technical, or material support:

Brittain, Pickthorn, Lin, Martin.

Supervision: Bakri, Ferrara, Brittain, Lin, Martin.

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