A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT Study)

12-Month Data: Report 2

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Purpose: To report the findings at 1 year of a study comparing repeated intravitreal bevacizumab (ivB) and modified Early Treatment of Diabetic Retinopathy Study (ETDRS) macular laser therapy (MLT) in patients with persistent clinically significant diabetic macular edema (CSME).

Design: Prospective, randomized, masked, single-center, 2-year, 2-arm clinical trial.

Participants: A total of 80 eyes of 80 patients with center-involving CSME and at least 1 prior MLT.

Methods: Subjects were randomized to either ivB (6 weekly; minimum of 3 injections and maximum of 9 injections in the first 12 months) or MLT (4 monthly; minimum of 1 treatment and maximum of 4 treatments in the first 12 months).

Main Outcome Measures: The primary end point was the difference in ETDRS best-corrected visual acuity (BCVA) at 12 months between the bevacizumab and laser arms.

Results: The baseline mean ETDRS BCVA was 55.7±9.7 (range 34–69) in the bevacizumab group and 54.6±8.6 (range 36–68) in the laser arm. The mean ETDRS BCVA at 12 months was 61.3±10.4 (range 34–79) in the bevacizumab group and 50.0±16.6 (range 8–76) in the laser arm ($P = 0.0006$). Furthermore, the bevacizumab group gained a median of 8 ETDRS letters, whereas the laser group lost a median of 0.5 ETDRS letters ($P = 0.0002$). The odds of gaining ≥10 ETDRS letters over 12 months were 5.1 times greater in the bevacizumab group than in the laser group (adjusted odds ratio, 5.1; 95% confidence interval, 1.3–19.7; $P = 0.019$). At 12 months, central macular thickness decreased from 507±145 μm (range 281–900 μm) at baseline to 378±134 μm (range 167–699 μm) ($P<0.001$) in the ivB group, whereas it decreased to a lesser extent in the laser group, from 481±121 μm (range 279–844 μm) to 413±135 μm (range 170–708 μm) ($P = 0.02$). The median number of injections was 9 (interquartile range [IQR] 8–9) in the ivB group, and the median number of laser treatments was 3 (IQR 2–4) in the MLT group.

Conclusions: The study provides evidence to support the use of bevacizumab in patients with center-involving CSME without advanced macular ischemia.

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Diabetic maculopathy is responsible for the majority of visual loss in patients with diabetic retinopathy.[1–4] Strict glycemic and blood pressure (BP) control remain the most effective interventions to date.[5,6] The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that laser photocoagulation reduced the risk of moderate visual loss in patients with clinically significant macular edema (CSME) by approximately 50% (from 24% to 12%) at 3 years, although visual acuity (VA) improvement was observed in less than 3% of cases (15-letter gain at 3 years).[7] However, this apparent modest level of improvement may largely be due to the fact that the majority of subjects (85%) had good entry vision (≥20/40), and it may be more meaningful that 40% of those with entry VA <20/40 improved 1 or more lines.[7]

Twenty-five years later, macular laser therapy (MLT) remains the standard-of-care treatment for diabetic macular edema (DME), despite studies of other therapeutic op-

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Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 1
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

tions.[8–16] Intravitreal triamcinolone acetonide (ivT) may improve vision and reduce macular thickness, but less than MLT,[10–12] and oral protein kinase C inhibitors may delay progression to center-involving CSME and reduce the rate of moderate visual loss from 9.1% to 5.5%.[13–15] Monthly injections of ranibizumab (0.5 mg in 0.05 ml) in the RESOLVE study resulted in a mean gain of 10 letters in ETDRS VA compared with patients randomized to placebo rather than MLT (Safety and efficacy of ranibizumab treatment in patients with diabetic macular edema: 12-month results of the Resolve Study. Invest Ophthalmol Vis Sci 2009;50: E-Abstract 4331). The Ranibizumab for Edema of the mAcula in Diabetes (READ2) study showed a 7.2-letter gain at 6 months in subjects receiving ranibizumab alone, compared with 3.8 letters in patients receiving combined MLT and 3 monthly ranibizumab injections, and a 0.4-letter loss in subjects receiving only MLT.[17]

Several retrospective uncontrolled case series with limited follow-up and variable treatment regimens have reported favorable effects of intravitreal bevacizumab (ivB) in the management of nonischemic DME.[18,19] Prospective, consecutive, noncomparative case series, with variable follow-up ranging from 6 weeks to 12 months, have provided more reliable data suggesting a beneficial effect of ivB in patients with chronic diffuse DME.[20,21] A prospective randomized 3-arm trial (1.25 mg ivB alone, ivB in combination with ivT, and MLT) in treatment-naïve patients with CSME reported findings at 12 weeks after single treatments.[22] The demonstration that a single ivB injection yielded better visual outcome in comparison with MLT (although it was not associated with a significant decrease in central macular thickness [CMT]), with no additive effect noted with ivT, led the investigators to repeat the study with more patients, repeat treatments, and longer follow-up.[23] Retreatments were performed at 12-week intervals when required. Findings at 36 weeks included a VA improvement of more than 2 Snellen lines in 37%, 25%, and 15% of patients in the ivB, ivB/ivT, and MLT groups, respectively.[23] A significant reduction of CMT in relation to the baseline measurement was observed only at 6 weeks in all groups.[23]

We have undertaken a prospective, single-center, randomized 2-year trial, enrolling patients with center-involving CSME who have received at least 1 prior MLT, to compare the efficacy of repeated ivB with 4 monthly modified ETDRS macular laser treatments (Diabetic macular edema: a prospective randomized trial of management with intravitreal bevacizumab (Avastin) versus conventional laser therapy: a description of methodology. Invest Ophthalmol Vis Sci 2008;49: E-Abstract 3505). Report 1 detailed our assessment of macular perfusion with fundus fluorescein angiography (FFA) at the 4-month time point in both study arms.[24] This report describes the 12-month study findings.

Patients and Methods

The protocol of the study adhered to the provisions of the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all patients. The study was undertaken at Moorfields Eye Hospital, London, United Kingdom.

Patient Eligibility

The following criteria were used to guide patient enrollment:

(A) *Inclusion criteria*: (1) patients of either gender aged ≥18 years; (2) diabetes mellitus (type 1 or 2); (3) best-corrected visual acuity (BCVA) in the study eye between 35 and 69 ETDRS letters at 4 m (Snellen equivalent ≥6/60 or ≤6/12); (4) center-involving CSME with CMT on optical coherence tomography (OCT) of ≥270 μm; (5) media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus imaging; (6) at least 1 prior MLT; (7) intraocular pressure (IOP) <30 mmHg; (8) ability to return for regular study visits; (9) fellow eye BCVA ≥3/60; and 10) fellow eye has received no anti-vascular endothelial growth factor (VEGF) treatment within the past 3 months and no expectation of such treatment during the study.

(B) *Exclusion criteria* (ocular criteria were applied to the *study eye only*): (1) macular ischemia (foveal avascular zone [FAZ] ≥1000 μm greatest linear dimension (GLD) or severe perifoveal intercapillary loss on FFA); (2) macular edema due to a cause other than DME; (3) coexistent ocular disease: (i) a preexisting ocular condition that was likely to preclude VA improvement despite resolution of macular edema (e.g., foveal atrophy, dense subfoveal hard exudates, marked cataract, amblyopia) or (ii) an ocular condition that may affect macular edema or alter VA during the course of the study (e.g., retinal vascular occlusion, ocular inflammatory disease, neovascular glaucoma, Irvine-Gass syndrome); (4) any treatment for DME in the preceding 3 months; (5) panretinal photocoagulation within 3 months of enrollment or anticipated 6 months thereafter; (6) proliferative diabetic retinopathy except for tufts of new vessels elsewhere <1 disc in area with no vitreous hemorrhage; (7) hemoglobin A1c (HbA1c) >11.0%; (8) medical history of chronic renal failure requiring dialysis or kidney transplantation; (9) BP >170/100 mmHg; (10) any thromboembolic event within 6 months, unstable angina, or evidence of active ischemia on electrocardiogram (ECG) at time of screening; (11) major surgery within 28 days of randomization or planned during the subsequent 12 months; (12) participation in an investigational drug trial within 30 days of randomization (or any time during the study); (13) systemic anti-VEGF or pro-VEGF treatment within 3 months of enrollment; (14) pregnancy, breast feeding, or intention to become pregnant within the study period; (15) intraocular surgery within 3 months of randomization; (16) aphakia; (17) uncontrolled glaucoma; and (18) significant external ocular disease.

Baseline Evaluation

After informed consent, medical and ophthalmic history was recorded and ophthalmologic examination was performed, including BCVA using ETDRS VA charts undertaken by a masked optometrist, applanation tonometry, and anterior segment and dilated slit-lamp biomicroscopic examination (including clinical grading of lens opacity). All subjects had standard ETDRS 7 field fundus photographs,[25] FFA, and OCT imaging (Stratus OCT 3000, Carl Zeiss Ophthalmic Systems Inc., Humphrey Division, Dublin, CA). Retinal thickness was measured in a circle (6.0 mm in diameter) centered on the point of fixation. The mean thickness of the 1-mm circle centered on the fovea (CMT) was recorded and used for statistical analysis. Retinal nerve fiber layer (RNFL) assessment commenced after recruitment started (and is therefore absent in

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 2
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

some patients) following the published literature investigating a possible adverse effect of bevacizumab on retinal ganglion cells.[26,27] Fundus photography, FFA, and OCT imaging were performed by masked investigators. All patients had their BP, HbA1c, and ECG recorded.

Randomization

Patients were randomized into 2 groups by means of an in-house computerized randomization program. The research investigator was not involved in the randomization process. Patients were stratified for BCVA, with the aim being that both groups would have comparable mean baseline BCVAs. If both eyes were eligible for enrollment, the eye with the worst VA was randomized.

Follow-up Visits

Laser Arm. All patients in the laser arm underwent modified ETDRS MLT at their baseline visit or within 7 days of randomization. Subjects were subsequently reviewed every 4 months (16 weeks, 32 weeks, and 48 weeks), with an end of year 1 visit at 52 weeks. Retreatment (16-, 32-, and 48-week time points) was performed if clinically indicated by ETDRS guidelines.[7] Modified ETDRS MLT comprised 50 μm argon laser spot size, laser applied only greater than 500 μm from the edge of the FAZ, with focal treatment aiming to cause mild blanching of the retinal pigment epithelium and not darkening/whitening of microaneurysms. Areas of diffuse leakage or nonperfusion were similarly treated in a grid pattern. At each visit, a full history was taken and a complete ocular examination was performed (including IOP and dilated fundoscopy); BP was measured; ETDRS BCVA was recorded by an optometrist; and 7-field color fundus photography, FFA, and OCT (CMT and RNFL) were undertaken. In addition, HbA1c and an ECG were recorded at the 52-week visit.

Bevacizumab Arm. All patients in the ivB arm underwent an injection at their baseline visit or within 7 days of randomization (1.25 mg in 0.05 ml). Subjects were subsequently reviewed every 6 weeks (6, 12, 18, 24, 30, 36, 42, and 48 weeks), with an end of year 1 visit at 52 weeks. After baseline ivB, patients received 2 further ivB injections (6- and 12-week time points). Subsequent ivB injections were guided by an OCT-based retreatment protocol. In brief, if the thinnest recorded CMT was less than 270 μm at 18 weeks, then treatment was continued only if macular thickness was not "stable." If CMT was greater than 270 μm at 18 weeks and subsequent visits, then ivB injections were administered until a "stable" macular thickness was attained. "Stable macular thickness" was defined as 3 consecutive visits with the CMT within 20 μm of the patient's thinnest recorded CMT. Patients could thereby receive a minimum of 3 injections and a maximum of 9 injections in the first 12 months.

At each visit, a full history was taken, ETDRS BCVA was recorded by a clinical investigator, and a complete ocular examination (including anterior chamber reaction, IOP, and dilated fundoscopy) and OCT (CMT and RNFL) were performed. In addition, at the 18-, 36-, and 52-week visits, BP was measured, ETDRS BCVA was recorded by a masked optometrist, and 7-field color fundus photography and FFA were undertaken. At the 52-week visit, HbA1c and an ECG were also recorded.

Surgical Technique

Bevacizumab (1.25 mg in 0.05 ml) (Avastin; Roche Registration Limited, UK) was prepared by Moorfields Pharmaceuticals (London, UK) as a prefilled syringe containing 0.13 ml. In a designated intravitreal treatment room, under sterile conditions, using topical anesthesia and povidone-iodine 5% into the conjunctival sac and onto the lid margins, and following application of a drape and insertion of a lid speculum, injections were undertaken with a 30-gauge needle through the supra- or infratemporal quadrant, with a drop of ofloxacin placed in the fornix at the end of the procedure. Patency of the central retinal artery was determined by indirect ophthalmoscopy and VA of hand movements or better. The IOP was checked 30 minutes after the injection, and if the pressure was increased ($\geq$30 mmHg) appropriate treatment was commenced. After the injection, topical ofloxacin was instilled 4 times per day for 4 days.

Outcome Measures

Comparison of the 2 groups was at equivalent but not always identical time points. These were at baseline (0 months), 4 months (16 weeks in the laser arm, 18 weeks in the ivB arm), 8 months (32 weeks in the laser arm, 36 weeks in the ivB arm), and 12 months (52 weeks in the laser and ivB arms).

The primary outcome measure of the trial was a comparison of the mean ETDRS BCVA at 12 months between the ivB and laser arms. The secondary outcome measures relating to efficacy were a comparison between both groups at 12 months with regard to (i) mean CMT; (ii) mean change in CMT; (iii) mean change in ETDRS BCVA; (iv) the proportion of patients who gained $\geq$15 and $\geq$10 ETDRS letters (improvement); (v) the proportion of patients who lost $<$15 ETDRS letters (stabilization); (vi) the proportion of patients who lost $\geq$30 ETDRS letters; and (vii) ETDRS grading of retinopathy severity.

The secondary outcome measures relating to safety were a comparison between both arms at 12 months with regard to (i) GLD of the FAZ, area of the FAZ, and perifoveal capillary loss (PFCL) (the methodology of determining these parameters has been previously described in detail);[24] (ii) RNFL thickness; (iii) other ocular side effects; and (iv) systemic side effects, including thromboembolic events, BP, and ECG findings.

Sample Size

A mean gain of 1.7 ETDRS letters in the MLT group of a previous randomized clinical trial at 12 months was used to power the laser arm of the study.[12] Powering for the bevacizumab group was based on a pilot study of ranibizumab for CSME that reported a mean gain of 10.0 ETDRS letters at 3 months.[16] Therefore, to have 80% power to detect a difference of 8.3 ETDRS letters (the difference between the mean of the 2 groups [1.7 vs. 10.0]) in the mean BCVAs of the 2 groups as significant (at the 2-sided 5% level), with an assumed common standard deviation of 12.3, the sample size required in each group was 36 patients. Forty patients per treatment group were required if one assumed a 10% dropout rate.

Masking

Although the patient and the study physician were not masked to the therapeutic modality, the study optometrist, OCT technician, photographer, graders performing assessment of the FAZ and ETDRS retinopathy grading, and study statistician were all masked to the patient randomization.

Statistical Analysis

Statistical analyses were performed with STATA 10.0 (StataCorp LP, College Station, TX) for Windows with the level of statistical significance set at $P<0.05$. Descriptive statistics have been used to document comparability of baseline characteristics. All random-

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 3
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

ized subjects were included in the efficacy analyses; intention-to-treat analysis based on the last-observation-carried-forward method was used. In addition, available case analysis was also undertaken to ensure the outcomes were comparable irrespective of the statistical technique used.

Analysis of covariance statistics were used to assess whether any observed differences between the 2 groups in primary and secondary efficacy outcomes at 12 months were statistically significant. Paired *t* tests were used to compare BCVA and CMT at 12 months with baseline values within each group. The treatment effect was estimated in terms of the odds ratio for gaining ≥10 ETDRS letters with 95% confidence intervals. Adjustment was made for baseline BCVA (because it was a stratification variable for randomization) and duration of CSME, which differed considerably between the treatment groups. In addition, we tested whether the apparent treatment effect was simply a result of higher cataract extractions in the bevacizumab group by a sensitivity analysis excluding subjects who had undergone cataract extraction.

With respect to safety outcomes, between-group comparisons were made using analysis of covariance for GLD and area of the FAZ, and a 2-sample Wilcoxon rank-sum (Mann–Whitney) test was used for PFCL and ETDRS retinopathy severity grading. Paired *t* tests were used to compare baseline GLD and area of the FAZ with 12-month values within each treatment group. The area of the FAZ data were log transformed before analysis because of skewness.

Results

Eighty eyes of 80 patients were enrolled. The first patient was recruited in May 2007 and the final patient had the 52-week visit in August 2009. The mean age of the patients was 64.2 ± 8.8 years (range 40–86 years), with 25 female (31%) and 55 male (69%) subjects. Thirty-eight patients were randomized to the laser group, and 42 patients were randomized to the bevacizumab group. Fifty-six patients were screened who did not satisfy the criteria for enrollment; the most common criteria that were not met were those relating to VA, FFA (macular ischemia), CMT, and cardiac ischemia (ECG changes). Results are summarized in Tables 1 to 9 (Tables 7, 8, and 9 are online only [available at http://aaojournal.org]).

The baseline characteristics of each treatment group are summarized in Tables 1 to 3 and 5. Except for the duration of CSME, there were no clinically significant differences observed at baseline between treatment arms, including demographic characteristics, BP, HbA1c, BCVA, CMT, and retinopathy grading. The mean ETDRS BCVA was 55.7±9.7 (range 34–69) in the bevacizumab group and 54.6±8.6 (36–68) in the laser arm, with the mean CMT being 507±145 μm (range 281–900) in the bevacizumab group and 481±121 μm (279–844) in the laser arm. In the bevacizumab group, the mean duration of diabetes and median duration of

Table 1. Non-Ocular Baseline Characteristics of the Two Treatment Groups

	Bevacizumab (ivB) Group	Laser (MLT) Group
No. of patients (eyes)	42	38
Male/female	30/12	25/13
Mean age (yrs)	64.9±9.4	63.5±8.1
Ethnicity:		
Asian or Asian British	8	17
Black or black British	8	5
White or white British	24	15
Other	2	1
Type 1 diabetes	4	4
Type 2 diabetes	38	34
Mean duration of DM (mos)	162±100 (range 11–444)	177±95 (range 7–360)
Mean HbA1c (%)	7.6±1.4 (range 5.3–10.9)	7.5±1.2 (range 5.4–10.6)
Mean systolic BP (mmHg)	138±19	142±16
Mean diastolic BP (mmHg)	76±10	75±7

BP = blood pressure; DM = diabetes mellitus; HbA1c = hemoglobin A1c; ivB = intravitreal bevacizumab; MLT = macular laser therapy.

Table 2. Ocular Baseline Characteristics of the Two Treatment Groups

	Bevacizumab (ivB) Group	Laser (MLT) Group
Study eye (left/right)	20/22	18/20
Median and [IQR] of duration of CSME (mos)	24 [18–48]	36 [24–55]
Median and [IQR] of No. of prior MLTs	3 [2–4]	3.5 [2–5]
Mean CMT (μm)	507±145 (range 281–900)	481±121 (range 279–844)
Previous vitrectomy	1 (42 mos ago)	0
Pseudophakic	5	8
Phakic	37	30

CMT = central macular thickness; CSME = clinically significant macular edema; IQR = interquartile range; ivB = intravitreal bevacizumab; MLT = macular laser therapy.

Table 3. Early Treatment of Diabetic Retinopathy Study Retinopathy Severity Level in the Laser and Bevacizumab Groups at Baseline and 12 Months

	Bevacizumab (ivB) Group	Laser (MLT) Group
Retinopathy severity at baseline		
Level 35	8	7
Level 43	21	15
Level 47	8	7
Level 53	3	7
Level 65	1†	1†
(No. of patients)	(n = 41)*	(n = 37)*
Retinopathy severity at 12 mos		
Level 35	12	6
Level 43	24	19
Level 47	3	6
Level 53	2	4
Level 65	0	1†
(No. of patients)	(n = 41)	(n = 36)

ivB = intravitreal bevacizumab; MLT = macular laser therapy.
Level 35 = mild NPDR; Level 43 = moderate NPDR; Level 47 = moderately severe NPDR; Level 53 = severe NPDR; Level 65 = moderate (non-high risk) proliferative diabetic retinopathy.
*The baseline color fundus photographs were of inadequate quality to grade in 1 patient in each treatment group.
†One patient in each group at baseline had persistent inactive new vessels elsewhere despite previous panretinal photocoagulation. At 12 months, these vessels had resolved in the patient in the ivB group (level 65 to level 35), whereas the laser group patient remained in the same severity level (level 65).

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 4
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

Table 4. Change in Early Treatment of Diabetic Retinopathy Study Retinopathy Severity Level in the Laser and Bevacizumab Groups between Baseline and 12 Months

Change in ETDRS Retinopathy Level	Bevacizumab	Laser	Total
−2	0	0	0
−1	1	3	4
0	29	27	56
1	7	4	11
2	2	1	3
3	0	0	0
4	1	0	1
Total No. of patients	40	35	75

ETDRS = Early Treatment of Diabetic Retinopathy Study.
The number of steps of change in severity was determined in each patient between baseline and 12 months in both treatment groups. For example, no change in severity level = 0; 1-step worsening in severity level of retinopathy (e.g., level 35 to level 43) = −1; and a 1-step improvement in severity (e.g., level 53 to level 47) = +1.

CSME in months was 162±100 (range 11–444) and 24 (interquartile range [IQR] 18–48), respectively, compared with 177 ± 95 (range 7–360) and 36 (IQR 24–55) in the laser arm. The previous number of laser treatments was comparable between the 2 groups; with a median of 3 (IQR 2–4) in the bevacizumab arm and 3.5 (IQR 2–5) in the laser group.

Two patients in the laser group did not complete 12 months of follow-up (1 patient moved away, and 1 patient could not be contacted). They were last reviewed at the 32-week time point, with these data being carried forward and an intention-to-treat analysis undertaken. All 42 patients in the ivB group completed the study. The median number of injections was 9 (IQR 8–9) in the bevacizumab group, and the median number of laser treatments was 3 (IQR 2–4) in the laser group.

Outcome Measures

Efficacy. The primary and secondary efficacy outcomes are summarized in Tables 3 to 5. There was a significant difference between the mean ETDRS BCVA at 12 months in the bevacizumab group (61.3±10.4; range 34–79) and laser arm (50.0±16.6; range 8–76) (P = 0.0006). Furthermore, the bevacizumab group gained a median of 8 (IQR 1–10) ETDRS letters, whereas the laser group lost a median of 0.5 (IQR −15 to 5) ETDRS letters (P = 0.0002). Figure 1 illustrates the mean change in BCVA from baseline at 3 comparable time points in the 2 treatment groups.

There was also a marked difference between the 2 treatment groups regarding the proportion of patients who gained, lost, or maintained vision (Table 5). Notably, the proportion of patients who gained ≥15 ETDRS letters (improvement) was 11.9% (5/42) in the bevacizumab group and 5.3% (2/38) in the laser arm (P = 0.43), with approximately one third of patients (31.0%, 13/42) gaining ≥10 ETDRS letters in the bevacizumab group compared with 7.9% (3/38) in the laser arm (P = 0.01). While 97.6% (41/42) in the bevacizumab arm and 73.7% (28/38) in the laser group lost <15 ETDRS letters (stabilization) (P = 0.002). No patients in the bevacizumab group lost ≥30 ETDRS letters (poor responders), whereas this outcome occurred in 5.3% (2/38) of laser arm subjects (P = 0.22).

The difference between both arms was also apparent with respect to CMT (Table 5). In the bevacizumab group, CMT had significantly decreased from 507±145 μm (range 281–900) at baseline to 378±134 μm (range 167–699) at 12 months (P<0.001), whereas over the same time period in the laser arm it had decreased to a lesser extent, from 481±121 μm (range 279–844) to 413±135 μm (range 170–708) (P = 0.02). The disparity between the 2 treatment groups was more evident when comparing the mean change in CMT over the 12 month period: −130±122 μm (range −475 to 92) in the bevacizumab arm and −68±171 (range −482 to 216) in the laser group (P = 0.06).

The corrected (baseline BCVA and duration of CSME) odds ratio estimate for gaining ≥10 letters in the bevacizumab group

Table 5. Efficacy Outcome Measures in the Two Treatment Groups

	Bevacizumab (ivB) Group	Laser (MLT) Group	P Value*
Baseline mean ETDRS BCVA	55.7±9.7 (range 34–69) (n = 42)	54.6±8.6 (range 36–68) (n = 38)	
12-mo mean ETDRS BCVA	61.3±10.4 (range 34–79) (n = 42)	50.0±16.6 (range 8–76) (n = 38)	0.0006
Median and [IQR] of change in ETDRS BCVA	8 [1–10] (n = 42)	−0.5 [−15 to 5] (n = 38)	0.0002
% of patients gaining ≥15 ETDRS letters	11.9 (5/42)	5.3 (2/38)	0.43
% of patients gaining ≥10 ETDRS letters	31.0 (13/42)	7.9 (3/38)	0.01
% of patients losing <15 ETDRS letters	97.6 (41/42)	73.7 (28/38)	0.002
% of patients losing ≥30 ETDRS letters	0 (0/42)	5.3 (2/38)	0.22
Baseline mean CMT (μm)	507±145 (range 281–900)	481±121 (range 279–844)	
12-mo mean CMT (μm)	378±134 (range 167–699)	413±135 (range 170–708)	
Mean change in CMT from baseline (μm)	−130±122 (range −475 to 92)	−68±171 (range −482 to 216)	0.06
Median and [IQR] of No. treatments	9 injections [8–9]	3 macular lasers [2–4]	

BCVA = best-corrected visual acuity; CMT = central macular thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; IQR = interquartile range; ivB = intravitreal bevacizumab; MLT = macular laser therapy.
*Intention-to-treat analysis based on the last-observation-carried-forward method; (2 laser arm subjects did not complete 12 months of follow-up and were last reviewed at the 32-week time point).

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 5
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

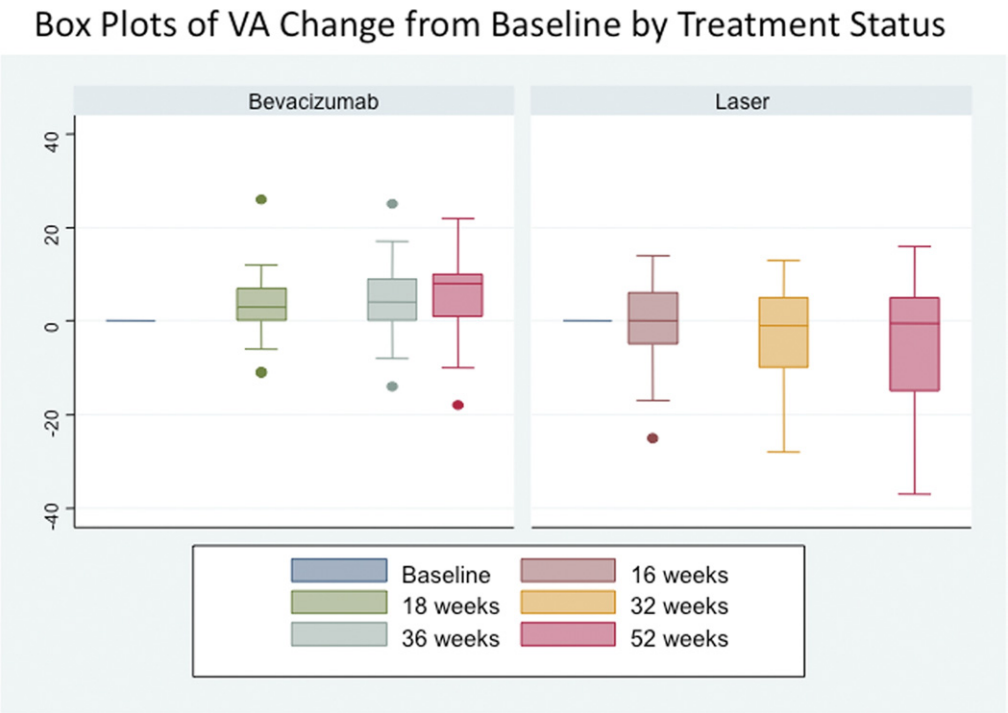

Figure 1. Box-plots of the mean change in best corrected visual acuity (BCVA) from baseline at 3 comparable time points (16 weeks in the laser arm, 18 weeks in the ivB arm; 32 weeks in the laser arm, 36 weeks in the ivB arm; and 52 weeks) in the 2 treatment groups. VA = visual acuity.

compared with the laser group was 5.1 (confidence interval, 1.3–19.7) ($P = 0.019$). Exclusion of those patients who had undergone cataract surgery resulted in a lowering of the adjusted odds ratio to 4.3 (1.1–17.4; $P = 0.04$). After adjusting for baseline BCVA, CMT, or duration of CSME, the mean BCVA at 12 months remained significantly different between the 2 treatment arms ($P<0.001$). To determine whether the greater number of patients in the bevacizumab group who had cataract surgery (n = 6) compared with the laser arm (n = 2) resulted in the BCVA difference between the 2 groups, an analysis including only the patients in the study who did not have cataract surgery was undertaken, which also demonstrated a significant difference between the groups ($P<0.001$).

The ETDRS retinopathy severity levels at baseline and 12 months in both treatment arms are shown in Table 3. In all patients throughout the study, retinopathy was graded as one of the following levels: 35 = mild nonproliferative diabetic retinopathy (NPDR), 43 = moderate NPDR, 47 = moderately severe NPDR, 53 = severe NPDR, and 65 = moderate (non-high risk) proliferative diabetic retinopathy. In the laser arm, the grading of retinopathy remained reasonably stable over the 12-month period (Table 3). In the bevacizumab arm, there was a trend suggesting a reduction in the level of severity over the 12 months (Table 3). The number of steps of change in severity has also been determined in each patient between baseline and 12 months in both treatment groups (Table 4). No change in severity level between baseline and 12 months was denoted as change = 0; a 1-step worsening in severity level of retinopathy (e.g., level 35 to level 43) was denoted as change = −1; and a 1-step improvement in severity (e.g., level 53 to level 47) was denoted as change = +1 (Table 4). By using a 2-sample Wilcoxon rank-sum (Mann–Whitney) test, there was no difference detected between the 2 treatment groups ($P = 0.13$).

Safety. The safety outcomes are summarized in Tables 6 to 9.

Macular Perfusion. Three parameters were determined on FFA, with no evidence of an adverse effect on macular perfusion of either treatment arm (Tables 6–8). At baseline, the mean GLD of the FAZ was 685±262 μm in the laser group and 737±262 μm in the bevacizumab group. Analysis of covariance revealed no evidence of a difference by treatment at 12 months ($P = 0.443$), with the mean GLD of the FAZ recorded as 640±225 μm in the laser group and 694±177 μm in the bevacizumab arm. The use of a paired t test also revealed no difference within each treatment group between baseline and 12 months ($P = 0.32$ laser group; $P = 0.35$ bevacizumab group).

At baseline, the median area of the FAZ was 0.36 mm^2 (IQR 0.21–0.46) in the laser group and 0.33 mm^2 (IQR 0.27–0.49) in the bevacizumab group. After log transformation of the data, analysis of covariance revealed no evidence of a difference by treatment at the 12-month time point ($P = 0.423$), with the median area of the FAZ recorded as 0.26 mm^2 (IQR 0.17–0.51) in the laser group and as 0.37 mm^2 (IQR 0.24–0.44) in the bevacizumab group. After log transformation, a paired t test revealed no difference within each treatment group between baseline and 12 months ($P = 0.20$ laser group; $P = 0.12$ bevacizumab group).

At baseline in the laser group, the number of subjects was evenly split between a grading of present and moderate PFCL (Table 7; available at http://aaojournal.org). However, at 12 months a greater proportion of subjects received a grading of present than moderate PFCL (Table 7; available at http://aaojournal.org). One patient in the laser group had progressed from a grade of moderate at baseline to severe PFCL at 12 months. At baseline and to a greater extent at 12 months in the bevacizumab group, a larger proportion of patients received a grading of present than moderate PFCL (Table 7; available at http://aaojournal.org). Three patients in the bevacizumab group had progressed from a grade of moderate at baseline to severe PFCL at 12 months. The number of steps of change in PFCL grade observed in each patient between baseline and 12 months in both treatment groups has been determined (Table 8; available at http://aaojournal.org). No change in grade between baseline and 12 months was denoted as change = 0; a

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 6
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

Table 6. Safety Outcome Measures in the Two Treatment Groups

	Bevacizumab (ivB) Group	Laser (MLT) Group	P Value
Cataract surgery in study eye during 12 mos (No. of patients)	6 (n = 42)	2 (n = 38)	
Baseline mean FAZ GLD (μm)	737±262 (n = 42)	685±262 (n = 38)	
12-mo mean FAZ GLD (μm)	694±177 (n = 40)	640±225 (n = 32)	0.44
Baseline median and [IQR] of the FAZ area (mm^2)	0.33 [0.27–0.49] (n = 42)	0.36 [0.21–0.46] (n = 37)	
12-mo. median and [IQR] of the FAZ area (mm^2)	0.37 [0.24–0.44] (n = 40)	0.26 [0.17–0.51] (n = 32)	0.42
PFCL grade at 12 mos compared with baseline	No change = 19 Worse = 10 Better = 11	No change = 15 Worse = 6 Better = 10	0.55
Baseline median and [IQR] RNFL thickness (μm)	95 [87–112] (n = 30)	100 [92–116] (n = 19)	
12-mo median and [IQR] RNFL thickness (μm)	94 [81–105] (n = 40)	98 [89–112] (n = 28)	
12-mo mean systolic BP (mmHg)	131±21 (n = 40)	135±17 (n = 36)	
12-mo mean diastolic BP (mmHg)	72±13 (n = 40)	75±8 (n = 36)	
Change in cardiovascular medication during study (No. of patients)	8 (n = 42)	8 (n = 36)	
12-mo mean HbA1c (%)	7.9±1.7 (range 5–14) (n = 41)	7.9±1.5 (range 6–12) (n = 36)	

BP = blood pressure; FAZ = foveal avascular zone; GLD = greatest linear dimension; IQR = interquartile range; ivB = intravitreal bevacizumab; MLT = macular laser therapy; PFCL = perifoveal capillary loss; RNFL = retinal nerve fiber layer.

1-step worsening in grade of PFCL (e.g., present to moderate) was denoted as change = −1; and a 1-step improvement in grade of PFCL (e.g., moderate to present) was denoted as change = +1 (Table 8; available at http://aaojournal.org). By using a 2-sample Wilcoxon rank-sum (Mann–Whitney) test, there was no difference detected between the 2 treatment groups ($P = 0.55$).

Retinal Nerve Fiber Layer. At baseline, the median RNFL thickness was 95 μm (IQR 87–112) in the bevacizumab group (n = 30) and 100 μm (IQR 92–116) in the laser group (n = 19) (Table 6). There was no clinically significant difference within or between the treatment groups at the 12-month time point, with the median RNFL recorded as 94 μm (IQR 81–105) in the bevacizumab arm (n = 40) and as 98 μm (IQR 89–112) in the laser arm (n = 28).

Other Ocular Side Effects. Ocular adverse events (AEs) and serious adverse events (SAEs) are summarized in Table 9 (available at http://aaojournal.org). There were 20 AEs in the bevacizumab group and 8 AEs in the laser arm over the 12 months, with the greater number in the bevacizumab group being secondary to ocular surface disturbances (15/20) related to intravitreal injections, in keeping with previous studies. The IOP-related AEs did not result in any permanent reduction in vision and did not require any ongoing medical therapy or surgical intervention. There was 1 SAE in the bevacizumab group and 3 SAEs in the laser arm. The patient who had an SAE related to IOP was subsequently diagnosed with ocular hypertension and is now receiving regular antiglaucoma medication. There were no cases of endophthalmitis, intraocular inflammation, or retinal detachment in the bevacizumab group.

Systemic Side Effects. Non-ocular AEs and SAEs are summarized in Table 9 (available at http://aaojournal.org). There were 4 non-ocular AEs in the bevacizumab group and 3 non-ocular AEs in the laser arm. There was no clinically significant difference between BP at baseline and 12 months in either treatment arm (Tables 1 and 6). One patient in the bevacizumab group was observed to have significantly elevated BP at the 52-week visit (210/110 mmHg). On review of this subject's chart he was also noted to have a highly elevated HbA1c at 52 weeks (14% compared with 6% at baseline), suggesting that poor compliance with his medication was likely. He has not been enrolled in the second year of the study. There were 2 non-ocular SAEs in the bevacizumab group and 4 non-ocular SAEs in the laser arm. There were no thromboembolic events or deaths in the bevacizumab arm. A masked cardiologist has compared baseline and 52 week ECGs in all subjects, with no evidence of active ischemia or silent cardiac events.

Discussion

This 2-arm randomized, controlled, masked, clinical trial has demonstrated that bevacizumab, at the 12-month time point, has a greater treatment effect than modified ETDRS MLT in patients with center-involving persistent CSME despite previous laser therapy. The primary end point of the study was met, with a highly significant difference between both groups in mean ETDRS BCVA at 12 months ($P = 0.0006$). The greater efficacy of bevacizumab was also observed with respect to the secondary end points: change in ETDRS BCVA from baseline ($P = 0.0002$), the proportion of patients gaining ≥10 ETDRS letters ($P = 0.01$), and the proportion of patients losing <15 ETDRS letters ($P = 0.002$). The proportion of patients gaining ≥15 ETDRS letters (12% compared with 5%) ($P = 0.43$) and losing ≥30 ETDRS letters (0% compared with 5%) ($P = 0.22$), although not reaching statistical significance, was in keeping with the other positive visual outcome measures.

These are significantly better visual outcomes than those associated with conventional ETDRS macular laser.[7] Al-

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 7
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

though modified ETDRS laser therapy has been reported to be associated with better results than conventional treatment, the results remain inferior to those reported in our study.[10–12,28] Intravitreal triamcinolone acetonide has now also been shown to be less effective than modified ETDRS MLT.[10–12] The treatment efficacy reported in the ranibizumab trials to date is comparable to that described in this report, although the RESOLVE study was uncontrolled with a monthly intravitreal injection protocol, and the Ranibizumab for Edema of the mAcula in Diabetes trial results are at 6 months with only a 3 monthly injection protocol in the MLT group (Safety and efficacy of ranibizumab treatment in patients with diabetic macular edema: 12-month results of the Resolve Study. Invest Ophthalmol Vis Sci 2009;50: E-Abstract 4331).[17] There is increasing evidence of a beneficial effect of bevacizumab in the treatment of DME.[18–23] A recent prospective randomized 3-arm trial (1.25 mg ivB alone, ivB in combination with ivT, and MLT) in treatment-naïve patients with CSME has reported positive visual outcomes similar to those of our trial.[23] However, the findings were at the 36-week time point, ETDRS VA charts were not used, retreatments were performed at 12-week intervals (a time period that would not be in keeping with the follow-up visits in the ETDRS study or the half-life of ivB),[7–9] and a significant reduction of CMT from baseline was only observed at 6 weeks in all groups.[23]

The good treatment effect we have shown with 6 weekly bevacizumab injections is in keeping with the efficacy demonstrated by a 6 weekly retreatment protocol in the ABC trial (Avastin [Bevacizumab] for choroidal neovascularization) investigating the use of bevacizumab in the management of neovascular age-related macular degeneration (Bevacizumab for neovascular age-related macular degeneration [ABC trial]: a randomized, double-masked study; number 4679 scientific paper; Retina Congress 2009) (The ABC Trial—a randomised, double-masked phase III study of the efficacy and safety of Avastin [Bevacizumab] intravitreal injections compared to standard therapy in subjects with choroidal neovascularisation [CNV] secondary to age-related macular degeneration [AMD]. Invest Ophthalmol Vis Sci 2007;48: E-Abstract 4536). A marked reduction in CMT was observed with repeated ivB injections over the course of our study, which correlated well with visual improvement. These findings may be related to our OCT-guided retreatment protocol that was designed to have a low threshold for repeat injections to guard against undertreatment, resulting in a median of 9 injections, with 75% of patients receiving ≥ 8 injections over 12 months. The subjects in the laser arm were also well treated, receiving a median of 3 treatments, with 75% undergoing ≥2 macular lasers. Further strengths of our study include the masked status of the optometrist, OCT technician, reading center graders, and statistician.

There were no serious ocular (including macular perfusion) or systemic safety concerns associated with repeated ivB identified in the study, having excluded patients with marked macular ischemia, poorly controlled diabetes and hypertension, or evidence of either recent thromboembolism or active cardiac ischemia. However, it should be borne in mind that clinical trials are not ideal sources of evidence on AEs, because AEs are typically uncommon and therefore unlikely to be seen with relatively small numbers of patients.

The decision on which therapies should be widely adopted is based principally on efficacy, safety, and cost. The cost to health care providers of bevacizumab is vastly lower compared with ranibizumab. Furthermore, the less frequent use of ivB will also provide financial, logistical, and professional savings. The importance of the additional benefits associated with bevacizumab is in light of the fact that current evidence suggests similar clinical outcomes to ranibizumab. Longer-term data from prospective randomized controlled studies on the use of ranibizumab are awaited to directly compare the efficacy of these 2 agents in DME.

In conclusion, the findings of our study support the use of bevacizumab in patients with persistent nonischemic center-involving CSME. It is notable that a significant benefit has been observed despite the relatively long duration of CSME and high number of previous laser treatments at baseline. The limitations of our clinical trial include the small number of patients and relatively short follow-up compared with the disease process being investigated and with respect to the recently identified continued beneficial effect of MLT at 3 years, with MLT being superior to ivT from the 16-month time point onward, but not at 12 months.[10,11,29] Further large multicenter studies are required with longer follow-up (at least 3 years) that also compare laser (standard care) with laser plus ivB (new therapy). Because of the chronic nature of the underlying disease process and the mechanism of action of anti-VEGF agents, monotherapy with anti-VEGF drugs is likely to be impractical, although the development of slow delivery systems may yet address this issue. Nevertheless, one would anticipate that treating patients with CSME with repeated ivB at an earlier time point, before irreversible structural damage has been sustained, will result in even better visual outcomes, and furthermore, that the more rapid reduction in macular edema compared with MLT may lead to superior longer-term VA.[30]

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Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 8
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

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This article contains additional online-only material. The following should appear online-only: Tables 7 to 9.

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Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 9
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

Table 7. Perifoveal Capillary Loss in the Laser and Bevacizumab Groups at Baseline and 12 Months

	Absent	Present	Moderate	Severe	Ungradeable
Laser baseline (n = 38)	1	18	18	0	1
Laser 12 mos (n = 32)	0	21	10	1	0
Bevacizumab baseline (n = 42)	0	23	19	0	0
Bevacizumab 12 mos (n = 40)	0	27	10	3	0

Table 8. Change in Perifoveal Capillary Loss Grade in the Laser and Bevacizumab Groups between Baseline and 12 Months

Change in PFCL Grade	Laser	Bevacizumab	Total
−2	0	0	0
−1	6	10	16
0	15	19	34
1	10	11	21
2	0	0	0
Total	31	40	71

PFCL = perifoveal capillary loss.

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 10
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

Table 9. Ocular and Non-Ocular Adverse Events and Serious Adverse Events in the Two Treatment Groups to 12 Months

	Bevacizumab (ivB) Group	Laser (MLT) Group
Ocular AEs		
1. Eye pain/irritation/watering during or after injection	8	0
2. Red eye after injection, including subconjunctival hemorrhage	7	0
3. Loss of ≥15 ETDRS letters	1	8
4. Transient increased IOP ≥30 mmHg	3	0
5. Floaters after injection	1	0
Non-ocular AEs		
1. Uncontrolled hypertension	1	0
2. Polymyalgia rheumatica	1	0
3. Intermittent claudication	1	0
4. Gastroenteritis	1	0
5. Anemia	0	1
6. Fall and wrist fractures	0	1
7. Vomiting after FFA	0	1
Total AEs	24	11
Ocular SAEs		
1. Increased IOP ≥45 mmHg	1*	0
2. Vitreous hemorrhage	0	1
3. Loss of >30 ETDRS letters	0	2
Non-ocular SAEs		
1. Admission for foot ulcer	1	1
2. Admission for cholecystectomy	1	0
3. Admission for fall/LOC	0	1
4. Worsening angina	0	1
5. Cerebrovascular accident	0	1
Total SAEs	3	7

AEs = adverse events; ETDRS = Early Treatment of Diabetic Retinopathy Study; FFA = fundus fluorescein angiography; IOP = intraocular pressure; ivB = intravitreal bevacizumab; LOC = loss of consciousness; MLT = macular laser therapy; SAEs = serious adverse events.
*Increased IOP after ivB; subsequently diagnosed with ocular hypertension and now receiving regular antiglaucoma medication.

Regeneron Pharmaceuticals, Inc. Exhibit 2058 Page 11
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739