A Phase II Randomized Clinical Trial of Intravitreal Bevacizumab for Diabetic Macular Edema

*Diabetic Retinopathy Clinical Research Network**

Objective: To provide data on the short-term effect of intravitreal bevacizumab for diabetic macular edema (DME).

Design: Randomized phase II clinical trial.

Participants: One hundred twenty-one eyes of 121 subjects (109 eligible for analysis) with DME and Snellen acuity equivalent ranging from 20/32 to 20/320.

Interventions: Random assignment to 1 of 5 groups: (A) focal photocoagulation at baseline (n = 19), (B) intravitreal injection of 1.25 mg of bevacizumab at baseline and 6 weeks (n = 22), (C) intravitreal injection of 2.5 mg of bevacizumab at baseline and 6 weeks (n = 24), (D) intravitreal injection of 1.25 mg of bevacizumab at baseline and sham injection at 6 weeks (n = 22), or (E) intravitreal injection of 1.25 mg of bevacizumab at baseline and 6 weeks with photocoagulation at 3 weeks (n = 22).

Main Outcome Measures: Central subfield thickness (CST) on optical coherence tomography and best-corrected visual acuity (VA) were measured at baseline and after 3, 6, 9, 12, 18, and 24 weeks.

Results: At baseline, median CST was 411 μm and median Snellen VA equivalent was 20/50. Compared with group A, groups B and C had a greater reduction in CST at 3 weeks and about 1 line better median VA over 12 weeks. There were no meaningful differences between groups B and C in CST reduction or VA improvement. A CST reduction $>$ 11% (reliability limit) was present at 3 weeks in 36 of 84 (43%) bevacizumab-treated eyes and 5 of 18 (28%) eyes treated with laser alone, and at 6 weeks in 31 of 84 (37%) and 9 of 18 (50%) eyes, respectively. Combining focal photocoagulation with bevacizumab resulted in no apparent short-term benefit or adverse outcomes. Endophthalmitis developed in 1 eye. The following events occurred during the first 24 weeks in subjects treated with bevacizumab without attributing cause to the drug: myocardial infarction (n = 2), congestive heart failure (n = 1), elevated blood pressure (n = 3), and worsened renal function (n = 3).

Conclusion: These results demonstrate that intravitreal bevacizumab can reduce DME in some eyes, but the study was not designed to determine whether treatment is beneficial. A phase III trial would be needed for that purpose. *Ophthalmology 2007;114:1860–1867 © 2007 by the American Academy of Ophthalmology.*

Macular edema is a major cause of central vision impairment in patients with diabetic retinopathy. To date, demonstrated means to reduce the risk of vision loss from diabetic macular edema (DME) include focal laser photocoagulation,[1,2] intensive glycemic control,[3] and blood pressure (BP) control.[4] In the Early Treatment Diabetic Retinopathy Study (ETDRS), focal photocoagulation of eyes with macular edema reduced the risk of moderate visual acuity (VA) loss (defined as a loss of $\geq$15 letters) by approximately 50% (from 24% to 12%) 3 years after randomization.[1] Among eyes with center-involved macular edema and baseline acuity worse than a Snellen equivalent of 20/40 that were treated with focal photocoagulation, 15-letter improvement rates were 11% at 1 year and 16% at 3 years (computed from ETDRS dataset by the authors).

The low frequency of improvement after focal laser photocoagulation for DME has prompted interest in other treatment modalities, including intravitreal triamcinolone acetonide,[5] oral protein kinase C β inhibitors,[6,7] pars plana vitrectomy,[8] and intravitreal aptamers[9] or antibodies directed against vascular endothelial growth factor (VEGF).[10,11]

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*See "Appendix 2" (available at http://aaojournal.org) for a complete list of the Network's members participating in the trial.

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Bevacizumab is a humanized monoclonal antibody that competitively inhibits all isoforms of the VEGF-A family in the extracellular space. Although bevacizumab is currently approved by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer, metastatic breast cancer, and non–small cell lung cancer, it is widely used as an off-label treatment for neovascular age-related macular degeneration (AMD) and retinal vascular disorders including retinal vein occlusion and DME.[12] Other anti-VEGF drugs, pegaptanib and ranibizumab, are currently approved by the FDA for the treatment of AMD.[13,14] Diabetic macular edema improvement has been reported with intravitreal pegaptanib in a 36-week phase II randomized trial[9] and with intravitreal ranibizumab in 2 case series.[10,15]

We conducted a pilot study to evaluate the short-term safety and effect of intravitreal bevacizumab, either alone or in combination with focal photocoagulation, in the treatment of DME.

Participants and Methods

This phase II randomized multicenter clinical trial was conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) at 36 clinical sites in the United States. The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by multiple institutional review boards. An investigational new drug application number (100 050) was obtained from the FDA for the protocol. Study oversight was provided by an independent data and safety monitoring committee. The study is listed on http://www.clinicaltrials.gov (NCT00336323). The protocol, which is available on the DRCR.net Web site (http://www.drcr.net), is summarized below.

Study Objectives

The overall study objective was to provide pilot data on the short-term effects of intravitreal injection(s) of bevacizumab, alone or with focal photocoagulation, for DME. Specific study questions included:

1. Does 1.25 mg of intravitreal bevacizumab reduce optical coherence tomography (OCT)–measured retinal thickening in DME?
2. Does 2.5 mg of intravitreal bevacizumab reduce OCT-measured retinal thickening in DME?
3. Does 2.5 mg of intravitreal bevacizumab produce a greater shorter-term reduction in OCT-measured retinal thickening from DME than 1.25 mg of intravitreal bevacizumab?
4. What is the duration of reduction in OCT-measured retinal thickening after the initial injection of intravitreal bevacizumab?
5. What is the duration of reduction in OCT-measured retinal thickening after the second injection of intravitreal bevacizumab?
6. Is there a greater reduction in OCT-measured retinal thickening using intravitreal bevacizumab followed by focal photocoagulation compared with intravitreal bevacizumab alone?

Study Population

Eligible subjects were at least 18 years old and had type 1 or type 2 diabetes. The major eligibility criteria for the study eye included (1) best-corrected electronic ETDRS[16] VA letter score $\geq$ 24 (20/320 or better) and $\leq$ 78 (20/32 or worse), (2) definite retinal thickening due to DME involving the center of the macula based on clinical examination, (3) OCT central subfield thickness (CST) $\geq$ 275 μm, and (4) no history of treatment for DME at any time within the prior 3 months. A subject could have only one study eye; if both eyes were eligible at the time of study entry, the study eye was selected by the investigator and subject. Additional eligibility and exclusion criteria are listed in Table 1 (available at http://aaojournal.org).

Synopsis of Study Design

After eligibility was confirmed and informed consent was obtained, each study eye was randomly assigned with equal probability to 1 of 5 treatment groups on the DRCR.net Web site: (A) focal photocoagulation at baseline; (B) intravitreal injection of 1.25 mg of bevacizumab (Avastin, Genentech, Inc., South San Francisco, CA) at baseline and 6 weeks; (C) intravitreal injection of 2.5 mg of bevacizumab at baseline and 6 weeks; (D) intravitreal injection of 1.25 mg of bevacizumab at baseline and sham injection at 6 weeks; and (E) intravitreal injection of 1.25 mg of bevacizumab at baseline, focal photocoagulation at 3 weeks, and intravitreal injection of 1.25 mg of bevacizumab at 6 weeks (referred to as the bevacizumab + laser group).

Subjects in groups B, C, and D were masked to bevacizumab dose and were also masked to whether the injection at 6 weeks was bevacizumab or sham. Subjects were not masked as to whether focal photocoagulation was being received. Investigators were not masked, but in most cases, the VA testers, OCT technicians, and photographers were masked. Optical coherence tomography graders were masked.

The trial consisted of 2 phases. Efficacy was assessed over a 12-week period and safety over a 70-week period (only the first 24 weeks of follow-up are presented in this report). Follow-up visits were performed at 3, 6, 9, 12, 18, 24, 41, and 70 weeks. The primary outcome variables were OCT-measured retinal thickening in the central subfield and best-corrected electronic ETDRS VA.

During the first 12 weeks of the study, treatment was administered as listed above by treatment group; no other treatment for DME was permitted in the study eye. At 12 weeks, additional treatment was deferred in eyes in which the central subfield was $<$250 μm or, if $\geq$250 μm, the central subfield thickening had decreased by at least 50% from baseline. At 18 weeks, additional treatment was again deferred if either the central subfield was $<$250 μm or the central subfield was $\geq$250 μm and there was at least an additional 20% decrease in central subfield thickening from baseline. Eyes not meeting these criteria at 12 or 18 weeks were treated at investigator discretion. Eyes in treatment group A (focal photocoagulation at baseline) not meeting the deferral criteria could receive an intravitreal injection of 1.25 mg of bevacizumab at 12 and 18 weeks. After 24 weeks, treatment was at investigator discretion for all groups.

Treatment Protocols

The bevacizumab injection technique was standardized, based on investigator usual practices. Topical antibiotic drops, which could be used at the discretion of the investigator, were administered before 61% of injections (sham and true) on the same day as the injection. A previously unopened 4-ml (25 mg/ml) vial of bevacizumab was used for each injection, which was given within 6 hours of opening the vial in accordance with the package labeling, as required by the FDA. Using a sterile eyelid speculum and topical anesthesia, followed by preparation with povidone–iodine, bevacizumab in doses of 1.25 mg in 0.05 cm^3 or 2.5 mg in 0.1 cm^3

was injected using a 30-gauge needle on a 1-cm^3 syringe into the vitreous cavity through the pars plana 3.0 to 4.0 mm posterior to the limbus. At the discretion of the investigator, topical antibiotic eyedrops were prescribed to be used for up to 3 days (this was employed after 82% of injections, sham and true). The sham injection technique included the same preparation as for an intravitreal injection and utilization of a syringe without a needle; the syringe hub was pressed against the conjunctival surface to simulate the force of an actual injection.

The focal photocoagulation technique was modified from the original ETDRS protocol, as described previously and used in prior protocols.[17] Laser burns were less intense (gray) and were smaller (50 μm) than in the original ETDRS protocol (50–200 μm).[18] A fluorescein angiogram was used to guide treatment at the investigator's discretion in 51% of cases.

Examination Procedures

At baseline and each follow-up visit, best-corrected VA was measured at 3 m by a certified tester using an electronic procedure based on the ETDRS method (electronic ETDRS).[16] Standardized refraction was performed at baseline and 9 weeks and at other visits if there was a ≥10-letter decrease from baseline. At each visit, the subject was queried about adverse events and a clinical examination was performed by a certified investigator, including dilated slit-lamp examination, fundus examination, and intraocular pressure (IOP) measurement. Standard ETDRS 7-field color stereoscopic fundus photographs were obtained at baseline and sent to the DRCR.net Reading Center at the University of Wisconsin–Madison for grading. Hemoglobin A_{1c} was measured at baseline. Any untoward medical occurrence in a study subject, irrespective of whether the event was considered treatment related, was considered an adverse event and recorded.

Optical coherence tomography images were obtained at each visit after pupil dilation by a certified operator using the Stratus OCT machine (Carl Zeiss Meditec, Dublin, CA). Scans were 6 mm long and included the 6–radial line pattern (fast macular scan option with Stratus OCT) for quantitative measures and the crosshair pattern (6- to 12-o'clock–9- to 3-o'clock) for qualitative assessment of retinal morphology. The OCT scans were sent to the DRCR.net Reading Center for grading. For 10% of the 109 baseline scans and 12% of the 612 follow-up scans, the automated thickness measurements were judged by the Reading Center to be inaccurate, and center point thickness (usually manually measured) was used to impute a value for the central subfield (based on a correlation of the 2 measures of 0.98, as reported previously[19]). Retinal morphology was assessed at baseline from OCT images for cystoid abnormalities and subretinal fluid (SRF).

Statistical Methods

Statistical principles were not used to estimate the sample size, which was planned to be about 20 eyes per treatment group. Because the study was designed to generate hypotheses rather than test hypotheses, it was decided a priori to exclude from the efficacy analyses ineligible subjects (n = 9; see Fig 1 [available at http://aaojournal.org] for reasons), subjects with no follow-up (n = 2), and subjects who developed a major complication of the intravitreal injection affecting VA (n = 1; endophthalmitis). All subjects receiving study treatment were included in the safety analysis. The primary time point for analysis varied according to the objective of each analysis.

Normality of distributions was evaluated and parametric tests were deemed appropriate; therefore, continuous CST and VA outcome measures were assessed using least-squares regression models adjusted for baseline values. Results did not differ substantially when models included adjustments for other baseline characteristics. Medians and interquartile ranges have been reported to provide information on the distribution of the data. The bevacizumab groups were pooled to assess the effect of various baseline characteristics (CST, VA, age, gender, prior treatment, retinopathy severity, clinician classification of DME, and SRF) on retinal thickness and VA at 3 weeks using least-squares regression models adjusted for baseline values.

All P values are 2 tailed. SAS (version 9.0, SAS Institute, Cary, NC) was used for all analyses.

Results

Between June 5, 2006 and August 4, 2006, 121 subjects were randomized to the 5 treatment groups (one eye per subject) at 36 clinical sites. Of these 121 subjects, 109 met criteria for inclusion in the analyses (19–24 per group; exclusions detailed in Fig 1 [available at http://aaojournal.org]). Median age was 65 years, and 39% were women. The racial/ethnicity distribution was 76% white, 16% black, 6% Hispanic, 1% Asian, and 1% other. Type 2 diabetes was present in 93% and type 1 diabetes in 7%. Median Snellen equivalent VA in the 109 eyes was 20/50 (letter score, 64 [range, 26–78]), and median OCT CST was 411 μm (range, 275–785); 75 eyes (69%) had received prior treatment for DME. Additional baseline characteristics by treatment group are provided in Table 2 (available at http://aaojournal.org).

Follow-up and Treatment

Two subjects were dropped from the study before completing 12 weeks of follow-up. The overall visit completion rate was 93%, ranging from 83% to 98% in the 5 groups (Fig 1).

Deviations from the treatment protocol are indicated in Figure 1. No treatment for DME other than the randomized treatment was administered to any eye before the 12-week visit.

Effect of Treatment on Retinal Thickening and Visual Acuity during First 12 Weeks

Central subfield retinal thickness during the first 12 weeks is presented according to treatment group in Table 3. Compared with the laser-alone group, groups B and C both demonstrated a greater reduction in CST at 3 weeks (P = 0.009 and P<0.001, respectively) but only a trend towards a greater reduction at 6, 9, and 12 weeks (Table 3). For VA, groups B and C both had about a median 1-line improvement at the 3-week visit, which was sustained through 12 weeks and was greater than the change in VA in group A (P = 0.01 and P = 0.003, respectively; Table 4). Over the 12-week period, no meaningful differences were found comparing groups B and C with each other in reduction in central subfield thickening or improvement in VA (for change in central subfield thickening, Ps = 0.66, 0.49, 0.45, and 0.90, respectively, at 3, 6, 9, and 12 weeks; for change in VA, Ps = 0.42, 0.67, 0.48, and 0.82, respectively). At the 12-week visit, comparing groups B and E there were no meaningful differences in central subfield thickening or VA identified.

A reduction in CST exceeding 11% (the reliability limit for real change determined in another DRCR.net study[20]) was present at 3 weeks in 23 of 60 (38%) 1.25-mg bevacizumab–treated eyes (pooling groups B, D, and E), in 13 of 24 (54%) 2.5-mg bevacizumab–treated eyes, and in 5 of 18 (28%) eyes treated with laser alone. The respective proportions at 6 weeks were 22 of 61 (36%) 1.25-mg bevacizumab–treated eyes (pooling groups B, D, and E), 9 of 23 (39%) 2.5-mg bevacizumab–treated eyes, and 9 of 18

Table 3. Central Subfield Retinal Thickness during First 12 Weeks According to Treatment Group

	A, Laser at Baseline (n = 19)	B, 1.25 mg at 0+6 Weeks (n = 22)	C, 2.5 mg at 0+6 Weeks (n = 24)	D, 1.25 mg at Baseline Only (n = 22)	E, 1.25 mg at 0+6 Weeks/Laser at 3 Weeks (n = 22)
Baseline (μm) [median (quartiles)]	441 (354, 512)	397 (320, 538)	446 (342, 543)	406 (353, 520)	389 (308, 452)
Change from baseline (μm) [median (quartiles)]					
3 wks	+21 (−62, +79)	−35 (−155, +6)	−86 (−131, −11)	−3 (−49, +7)	−13 (−104, +26)
6 wks	−40 (−105, +73)	−35 (−112, +6)	−42 (−127, −10)	−17 (−58, +25)	−20 (−73, +35)
9 wks	−53 (−115, +53)	−74 (−113, −31)	−56 (−127, −20)	+5 (−34, +53)	−48 (−128, +33)
12 wks	−40 (−146, +85)	−56 (−120, −6)	−47 (−125, −16)	−5 (−41, +53)	−40 (−103, +33)
<250 μm or ≥50% reduction in retinal thickening					
3 wks	11%	37%	38%	10%	25%
6 wks	17%	30%	22%	19%	25%
9 wks	19%	38%	22%	10%	37%
12 wks	21%	33%	33%	14%	25%

Medians and interquartile ranges are reported rather than means and standard deviations because of the small sample size per group to present a better perspective on the distribution of the data and to minimize the effect of extreme values. Numbers of subjects completing each visit are given in Figure 1. In addition to the missed visits, 10 optical coherence tomography measurements were not done at completed visits (group A: 2 at 9 wks; group B: 2 at 3 wks, 2 at 6 wks; group C: 1 at 6 wks; group D: 1 at 3 wks, 1 at 6 wks, 1 at 9 wks).

(50%) eyes treated with laser alone. Twenty-five of 57 (44%) 1.25-mg bevacizumab–treated eyes, 14 of 23 (61%) 2.5-mg bevacizumab–treated eyes, and 9 of 17 (53%) eyes treated with laser alone had a reduction in CST exceeding 11% at one or both of the visits. As seen in Table 2 (available at http://aaojournal.org), at 12 weeks no more than a third of the eyes in each group met the protocol-specified criteria to defer further treatment (CST < 250 μm or a reduction from baseline in central subfield thickening by

Table 4. Visual Acuity during First 12 Weeks According to Treatment Group

	A, Laser at Baseline (n = 19)	B, 1.25 mg at 0+6 Weeks (n = 22)	C, 2.5 mg at 0+6 Weeks (n = 24)	D, 1.25 mg at Baseline Only (n = 22)	E, 1.25 mg at 0+6 Weeks/Laser at 3 Weeks (n = 22)
Baseline letter score [median (quartiles)]	64 (50, 70)	65 (60, 70)	63 (57, 71)	64 (52, 68)	66 (57, 72)
Distribution of change from baseline (letters) [median (quartiles)]					
3 wks	−2 (−7, +3)	+5 (−1, +8)	+6 (+1, +9)	+2 (0, +7)	0 (−6, +6)
6 wks	+1 (−6, +6)	+5 (−2, +12)	+6 (+2, +11)	+3 (−2, +6)	0 (−4, +6)
9 wks	+3 (−5, +6)	+7 (+2, +10)	+8 (+3, +12)	+1 (−3, +5)	−2 (−5, +11)
12 wks	−1 (−6, +5)	+5 (+1, +12)	+7 (+4, +11)	+4 (−3, +7)	0 (−5, +8)
Change from baseline [n (%)]					
3 wks					
≥15-letter improvement	1 (6)	1 (5)	0	2 (9)	1 (5)
≥10-letter improvement	1 (6)	4 (19)	4 (17)	2 (9)	2 (10)
Within ±9 letters	16 (89)	16 (76)	20 (83)	19 (86)	18 (90)
≥10 letters worse	1 (6)	1 (5)	0	1 (5)	0
6 wks					
≥15-letter improvement	1 (6)	2 (9)	1 (4)	1 (5)	1 (5)
≥10-letter improvement	2 (11)	7 (32)	7 (29)	3 (14)	3 (15)
Within ±9 letters	14 (78)	15 (68)	16 (67)	18 (82)	13 (65)
≥10 letters worse	2 (11)	0	1 (4)	1 (5)	4 (20)
9 wks					
≥15-letter improvement	1 (6)	3 (14)	3 (13)	3 (14)	3 (16)
≥10-letter improvement	3 (18)	6 (29)	9 (39)	3 (14)	5 (26)
Within ±9 letters	13 (76)	14 (67)	14 (61)	18 (86)	12 (63)
≥10 letters worse	1 (6)	1 (5)	0	0	2 (11)
12 wks					
≥15-letter improvement	1 (5)	3 (14)	3 (13)	2 (9)	3 (15)
≥10-letter improvement	3 (16)	7 (33)	6 (25)	2 (9)	4 (20)
Within ±9 letters	15 (79)	13 (62)	18 (75)	18 (82)	14 (70)
≥10 letters worse	1 (5)	1 (5)	0	2 (9)	2 (10)

Medians and interquartile ranges are reported rather than means and standard deviations because of the small sample size per group to present a better perspective on the distribution of the data and to minimize the effect of extreme values. Numbers of subjects for each visit are given in Figure 1. In addition to the missed visits, one group A subject did not complete visual acuity testing at the 9-wk visit.

at least 50%). Among eyes meeting the deferral criteria at 12 weeks, the deferral criteria were also met at 18 weeks in 2 of 4 eyes in group A, 5 of 7 eyes in group B, 1 of 8 eyes in group C, 2 of 3 eyes in group D, and 3 of 5 eyes in group E.

As seen in Tables 3 to 8 (the last 4 available at http://aaojournal.org), data do not suggest continued reduction in central subfield thickening or VA improvement in most eyes between 3 and 6 weeks or a more prolonged effect with the 2.5-mg dose than with the 1.25-mg dose. Among the 14 eyes in the 1.25-mg groups (B and D) and 13 eyes in the 2.5-mg group (C) that experienced a decrease from baseline to 3 weeks in CST exceeding 11%, there were more eyes in each group in which CST increased (>11%) between 3 and 6 weeks than decreased further. Among the 7 eyes in group B and 3 eyes in group C that experienced a decrease from 6 to 9 weeks in CST exceeding 11%, there were no eyes with a further decrease (>11%) between 9 and 12 weeks.

Subgroup Analyses of Pooled Bevacizumab Groups at 3 Weeks

The 4 bevacizumab groups (B, C, D, and E; n = 87) were pooled to compare differences in response at 3 weeks among subgroups of interest (Table 9 [available at http://aaojournal.org]). Eyes with thicker retinas at baseline experienced a greater absolute reduction in central subfield thickening ($P<0.0001$), but the association was less pronounced for a relative reduction in thickening (change in thickening relative to baseline thickening) ($P = 0.12$). Likewise, with VA, eyes with worse baseline VA showed greater improvement in VA at 3 weeks ($P = 0.006$), but the percent reduction in the VA deficit did not differ according to baseline acuity ($P = 0.40$). Change in central subfield thickening and change in VA from baseline to 3 weeks did not vary substantially according to subject age ($P = 0.44$ and $P = 0.23$, respectively), gender ($P = 0.55$ and $P = 0.37$), retinopathy severity ($P = 0.53$ and $P = 0.38$), or clinician categorization of DME as focal or diffuse ($P = 0.93$ and $P = 0.45$). There was a suggestion of greater effect on VA in eyes that had not been treated previously for DME compared with previously treated eyes ($P = 0.04$), but less so for central subfield thickening ($P = 0.16$). In eyes with SRF compared with eyes with no evidence of SRF, there was a suggestion of greater effect on change in VA ($P = 0.06$) but not on change in central subfield thickening ($P = 0.52$).

Adverse Effects

Endophthalmitis (due to coagulase-negative staphylococcus) developed in one subject after an intravitreal bevacizumab injection. A transient increase in IOP occurred in one subject 6 weeks after an initial 1.25-mg bevacizumab injection. There were no other cases of consequential treatment-related ocular adverse events, including no reported cases of uveitis.

Among the 107 subjects who received at least one bevacizumab injection, a myocardial infarction occurred in 2 and congestive heart failure in 1. One fatal myocardial infarction occurred in a 78-year-old man 73 days after the second injection of 1.25-mg bevacizumab, and a nonfatal myocardial infarction occurred in a 69-year-old man 5 days after an initial injection of 2.5-mg bevacizumab; both men had a history of coronary artery bypass surgery. The episode of congestive heart failure occurred in a 56-year-old woman who had a history of 3 similar episodes, 40 days after the second injection of 1.25-mg bevacizumab.

Three bevacizumab-treated subjects experienced elevation of BP (groups C, D, and E); 1 of these subjects had a history of hypertension. There were no significant differences in mean BP comparing the focal photocoagulation group with the bevacizumab groups (pooled) at the 3-, 6-, 9-, or 12-week visits. Other reported adverse events in bevacizumab-treated subjects included death due to pancreatic cancer (n = 1; group B), peripheral vascular disease (n = 1; group C), syncope (n = 1; group B), worsening of renal function (n = 3; groups C–E), and anemia (n = 4; groups B–E). In the 12 subjects who received only focal photocoagulation, there were no thromboembolic cardiovascular events; 1 case of anemia, 2 cases of peripheral vascular disease, 1 case of hypertension, and 1 case of worsening of renal function were reported.

Discussion

To assist in the development of a phase III randomized trial protocol, this study was designed to address 6 questions related to the short-term effect of intravitreal bevacizumab for DME plus provide preliminary ocular and systemic safety data.

1. Does 1.25-mg Intravitreal Bevacizumab Reduce Optical Coherence Tomography–Measured Retinal Thickening in Diabetic Macular Edema?/2. Does 2.5-mg Intravitreal Bevacizumab Reduce Optical Coherence Tomography–Measured Retinal Thickening in Diabetic Macular Edema?

Compared with a control group receiving focal photocoagulation, both the 1.25- and 2.5-mg bevacizumab–treated eyes had a greater reduction in central retinal thickness at 3 weeks. Eyes in the photocoagulation group demonstrated improvement in these parameters with longer follow-up. As a result, there were no meaningful differences in CST observed for bevacizumab relative to photocoagulation after the 3-week time point. Only about half of the eyes showed what was judged to be a response to intravitreal bevacizumab (exceeding an 11% reduction in retinal thickness compared with baseline) at either the 3- or 6-week visit. For VA, with both bevacizumab doses on average there was about 1 line greater improvement relative to photocoagulation throughout the 12 weeks.

3. Does 2.5-mg Intravitreal Bevacizumab Produce a Greater Shorter-Term Reduction in Optical Coherence Tomography–Measured Retinal Thickening from Diabetic Macular Edema than 1.25-mg Intravitreal Bevacizumab?

Comparisons of the 2.5- and 1.25-mg doses suggest that there is not likely a large difference in short-term effect between the 2 doses. However, no conclusions should be drawn about the long-term comparative effect of the 2 doses.

4. What Is the Duration of Reduction in Optical Coherence Tomography–Measured Retinal Thickening after the Initial Injection of Intravitreal Bevacizumab?/5. What Is the Duration of Reduction in Optical Coherence Tomography–Measured Retinal Thickening after the Second Injection of Intravitreal Bevacizumab?

The reduction in retinal thickness associated with bevacizumab at 3 weeks appeared to plateau or decrease in most eyes between the 3- and 6-week visits, suggesting that 6 weeks may be too long for an optimal initial injection interval. Four of 61 bevacizumab only–treated eyes (7%) showed a reduction in CST between 3 and 6 weeks, whereas 11 of the 61 eyes (18%) showed an increase in thickness between 3 and 6 weeks. After the second injection, 4 of 40 eyes (10%) had a decrease in thickness between the 9- and 12-week visits, whereas 7 of 40 (18%) had an increase, again suggesting that 6 weeks may be too long for an optimal second injection interval.

6. Is There a Greater Reduction in Optical Coherence Tomography–Measured Retinal Thickening Using Intravitreal Bevacizumab Followed by Focal Photocoagulation Compared with Intravitreal Bevacizumab Alone?

Combining photocoagulation with bevacizumab resulted in no apparent short-term benefit or adverse outcomes. Although this study demonstrated the feasibility for future protocols of including a group that receives intravitreal bevacizumab followed by focal photocoagulation at 3 weeks, the follow-up was too short to determine if combination therapy would be beneficial in either improving visual outcome or reducing the number of intravitreal injections required. A beneficial effect of focal photocoagulation could occur over a time longer than the duration of this study.

Comparison with Literature

Although reports in the literature note individual cases of short-term improvement in VA and reduction in OCT-measured retinal thickening after intravitreal injection of an anti-VEGF drug (bevacizumab, pegaptanib, or ranibizumab), none of these reports included subjects concurrently randomized to focal photocoagulation.[11,21]

Safety

The systemic use of bevacizumab has been associated with an increased risk of cerebrovascular and cardiovascular thromboembolic events (bevacizumab package insert). Although the intravitreal dose is 1/400 or less of the usual systemic dose, the possibility of a systemic adverse effect after an intravitreal bevacizumab injection nevertheless exists. According to the ranibizumab package insert, intravitreal ranibizumab has a "theoretical risk of arterial thromboembolic events," and in an ongoing study of ranibizumab delivered intravitreally to patients with neovascular AMD (SAILOR [Safety Assessment of Intravitreal Lucentis for Age-Related Macular Degeneration]), in a planned interim safety analysis performed on data from cohort 1, patients with an average follow-up of 230 days demonstrated a higher incidence of strokes in the 0.5-mg dose group than in the 0.3-mg group (1.2% vs. 0.3%, $P = 0.02$).[22]

Systemic safety evaluation of bevacizumab in the current study is limited by the small sample size and short follow-up. There were several cases of systemic cardiovascular or renal adverse effects, all of which occurred in subjects with related preexisting medical conditions, including 2 cases of myocardial infarction. In this study, there was 1 case of injection-related endophthalmitis in 185 injections, an uncommon but well-recognized complication of intravitreal injection, but no important ocular complications attributable to the drug. The follow-up of patients in published reports of the use of intravitreal bevacizumab in humans is too short to be conclusive regarding the ocular safety of intravitreal bevacizumab.[23–25]

This study was conducted to provide data to assist in the development of a phase III randomized clinical trial protocol and, by design, had a short follow-up and modest sample size. Therefore, definitive safety and effectiveness conclusions are limited. Although about half of eyes demonstrated an initial positive response to intravitreal bevacizumab (exceeding an 11% reduction in retinal thickness compared with baseline at either the 3- or 6-week visit), this response was similar to that observed in the laser group after more than 3 weeks. In addition, the magnitude of the response was not large for most subjects. Thus, these short-term results of the current study should not be generalized to conclude that there is a clinically meaningful benefit in treating DME with intravitreal bevacizumab or other anti-VEGF drugs. This determination of clinical benefit will require the conduct of a large phase III randomized clinical trial.

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Appendix 1

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Diabetic Retinopathy Clinical Research Network

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Appendix 2: Diabetic Retinopathy Clinical Research Network

Clinical Sites That Participated in This Protocol

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Table 1. Eligibility and Exclusion Criteria

Subject-level inclusion criteria
1. Age ≥ 18 yrs
2. Diagnosis of diabetes mellitus (type 1 or type 2)
3. At least one eye meets the study eye criteria listed below
4. Fellow eye meets criteria listed below

Subject-level exclusion criteria
1. Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant
2. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., unstable medical status including BP, cardiovascular disease, and glycemic control)
3. Participation in an investigational trial within 30 days of randomization that involved treatment with any drug that has not received regulatory approval at the time of study entry
4. Known allergy to any component of the study drug
5. BP > 180/110 (systolic above 180 or diastolic above 110)
6. Major surgery within 28 days before randomization or major surgery planned during the next 6 mos
7. Myocardial infarction, other cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 6 mos before randomization
8. Systemic anti-VEGF or pro-VEGF treatment within 3 mos before randomization
9. For women of childbearing potential: pregnant or lactating or intending to become pregnant within the next 6 mos
10. Subject is expecting to move out of the area of the clinical center to an area not covered by another clinical center during the first 6 mos of the study

Study eye inclusion criteria
1. Best-corrected electronic ETDRS VA letter score ≥ 24 (i.e., 20/320 or better) and ≤ 78 (i.e., 20/32 or worse) within 8 days of randomization
2. On clinical examination, definite retinal thickening due to DME involving the center of the macula
3. OCT central subfield ≥ 275 μm within 8 days of randomization
4. Media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs
5. If prior macular photocoagulation has been performed, the investigator believes that the study eye may benefit from additional photocoagulation

Study eye exclusion criteria
1. Macular edema is considered to be due to a cause other than DME
2. An ocular condition is present such that, in the opinion of the investigator, VA would not improve from resolution of macular edema (e.g., foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition)
3. An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter VA during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine–Gass syndrome)
4. Substantial cataract that, in the opinion of the investigator, is likely to be decreasing VA by ≥3 lines (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal)
5. History of treatment for DME at any time in the past 3 mos (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, anti-VEGF drugs, or any other treatment)
6. History of panretinal scatter photocoagulation within 4 mos before randomization
7. Anticipated need for panretinal scatter photocoagulation in the 6 mos after randomization
8. History of pars plana vitrectomy
9. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 6 mos or anticipated within the 6 mos after randomization
10. History of yttrium–aluminum–garnet capsulotomy performed within 2 mos before randomization
11. Aphakia
12. Uncontrolled glaucoma (in investigator's judgment)
13. Examination evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis

Fellow eye inclusion criteria
1. Best-corrected electronic ETDRS VA letter score ≥ 19 (i.e., 20/400 or better)
2. No anti-VEGF treatment within the past 3 mos and no expectation of such treatment in next 3 mos

BP = blood pressure; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; OCT = optical coherence tomography; VA = visual acuity; VEGF = vascular endothelial growth factor.

Table 2. Baseline Subject Data According to Treatment Group

	All (N = 109)	A, Laser at Baseline (n = 19)	B, 1.25 mg at 0+6 Weeks (n = 22)	C, 2.5 mg at 0+6 Weeks (n = 24)	D, 1.25 mg at Baseline Only (n = 22)	E, 1.25 mg at 0+6 Weeks/Laser at 3 Weeks (n = 22)
Gender (female) [n (%)]	43 (39)	9 (47)	6 (27)	9 (38)	9 (41)	10 (45)
Age (yrs) [median (quartiles)]	65 (57, 73)	64 (57, 72)	63 (54, 73)	68 (59, 75)	60 (54, 75)	67 (60, 71)
Race [n (%)]						
White	83 (76)	10 (53)	16 (73)	20 (83)	18 (82)	19 (86)
Black	17 (16)	7 (37)	3 (14)	2 (8)	3 (14)	2 (9)
Hispanic/Latino	7 (6)	2 (11)	2 (9)	2 (8)	0	1 (5)
Asian	1 (1)	0	0	0	1 (5)	0
Unknown/not reported	1 (1)	0	1 (5)	0	0	0
Diabetes type [n (%)]						
1	8 (7)	1 (5)	1 (5)	3 (13)	2 (9)	1 (5)
2	101 (93)	18 (95)	21 (95)	21 (88)	20 (91)	21 (95)
Duration of diabetes (yrs) [median (quartiles)]	17 (11, 23)	17 (13, 22)	15 (8, 22)	18 (12, 22)	17 (11, 25)	20 (7, 30)
Hemoglobin A_{1c} [median (quartiles)]*	6.9 (6.3, 8.1)	7.0 (6.5, 8.2)	7.4 (5.9, 7.8)	7.3 (6.4, 8.4)	6.7 (6.3, 7.4)	7.1 (6.2, 7.7)
Prior treatment for DME in study eye [n (%)]						
None	34 (31)	7 (37)	5 (23)	10 (42)	5 (23)	7 (32)
Focal photocoagulation alone	39 (36)	4 (21)	11 (50)	9 (38)	6 (27)	9 (41)
Focal photocoagulation plus other treatment	31 (28)	8 (42)	3 (14)	3 (13)	11 (50)	6 (27)
Other treatment without focal photocoagulation	5 (5)	0	3 (14)	2 (8)	0	0
Prior panretinal scatter photocoagulation [n (%)]	13 (12)	3 (16)	2 (9)	3 (13)	1 (5)	4 (18)
Baseline visual acuity						
Letter score [median (quartiles)]	64 (56, 71)	64 (50, 70)	65 (60, 70)	63 (57, 71)	64 (52, 68)	66 (57, 72)
Approximate Snellen score	$20/50^{-1}$	$20/50^{-1}$	20/50	$20/50^{-2}$	$20/50^{-1}$	$20/50^{+1}$
Lens status (phakic) [n (%)]	66 (61)	12 (63)	15 (68)	14 (58)	12 (55)	13 (59)
Retinopathy severity† (ETDRS severity scale) [n (%)]						
Mild NPDR (level 35)	14 (14)	1 (6)	6 (29)	3 (14)	0	4 (18)
Moderate NPDR (level 43)	15 (15)	5 (28)	3 (14)	1 (5)	3 (15)	3 (14)
Moderately severe NPDR (level 47)	36 (35)	5 (28)	6 (29)	8 (36)	8 (40)	9 (41)
Severe NPDR (level 53)	8 (8)	0	1 (5)	2 (9)	4 (20)	1 (5)
Mild PDR (levels 60 and 61)	24 (23)	4 (22)	5 (24)	6 (27)	5 (25)	4 (18)
Moderate PDR (level 65)	4 (4)	1 (6)	0	2 (9)	0	1 (5)
High-risk PDR (levels 71 and 75)	2 (2)	2 (11)	0	0	0	0
Character of DME‡ [n (%)]						
Typical/predominantly focal	20 (18)	6 (32)	5 (23)	2 (8)	3 (14)	4 (18)
Neither predominantly focal or diffuse	26 (24)	4 (21)	5 (23)	5 (21)	6 (27)	6 (27)
Typical/predominantly diffuse	63 (58)	9 (47)	12 (55)	17 (71)	13 (59)	12 (55)
OCT central subfield thickness (μm) [median (quartiles)]	411 (334, 505)	441 (354, 512)	397 (320, 538)	446 (342, 543)	406 (353, 520)	389 (308, 452)
OCT retinal volume§ (mm^3) [median (quartiles)]	8.6 (7.8, 10.1)	8.3 (7.3, 10.2)	9.5 (8.0, 10.3)	9.1 (8.0, 10.0)	8.9 (7.7, 10.0)	8.6 (7.7, 9.2)
Cystoid abnormalities on OCT‖ [n (%)]	106 (98)	18 (100)	22 (100)	24 (100)	21 (95)	21 (95)
Subretinal fluid on OCT¶ [n (%)]						
Definite, center	17 (16)	2 (11)	2 (9)	7 (29)	2 (9)	4 (18)
Definite, not center	3 (3)	0	1 (5)	1 (4)	0	1 (5)
Questionable	3 (3)	0	1 (5)	0	2 (9)	0
No evidence	85 (79)	16 (89)	18 (82)	16 (67)	18 (82)	17 (77)

DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; NPDR = nonproliferative diabetic retinopathy; OCT = optical coherence tomography.
*Missing for 8 subjects.
†Missing for 6 subjects.
‡Question on form: "Indicate how you would characterize type—focal vs. diffuse—in your own daily practice. You are free to use, or not use, OCT, fluorescein angiography, and/or fundus photos in addition to your clinical examination."
§Missing for 19 subjects.
‖Missing for 1 subject.
¶Missing for 1 subject.

Table 5. Duration of Bevacizumab Effect Based on Change in Central Subfield Thickness: Duration of Initial Injection, 1.25-mg Groups

	Change from Baseline to 3 Weeks		
	>11% Decrease (n = 14)	*Within ±11% (n = 22)*	*>11% Increase (n = 2)*
Change from 3 wks to 6 wks			
>11% decrease	1	2	1
Within ±11%	11	16	1
>11% increase	2	4	0

Change in central subfield thickness categorized according to whether it exceeded 11%, the reliability limit for real change determined in another Diabetic Retinopathy Clinical Research Network study.[20] Groups B and D pooled. N = 38 eyes with data at baseline, 3 wks, and 6 wks.

Table 6. Duration of Bevacizumab Effect Based on Change in Central Subfield Thickness: Duration of Initial Injection, 2.5-mg Group

	Change from Baseline to 3 Weeks		
	>11% Decrease (n = 13)	*Within ±11% (n = 10)*	*>11% Increase (n = 0)*
Change from 3 wks to 6 wks			
>11% decrease	0	0	0
Within ±11%	9	9	0
>11% increase	4	1	0

Change in central subfield thickness categorized according to whether it exceeded 11%, the reliability limit for real change determined in another Diabetic Retinopathy Clinical Research Network study.[20] Group C. N = 23 eyes with data at baseline, 3 wks, and 6 wks.

Table 7. Duration of Bevacizumab Effect Based on Change in Central Subfield Thickness: Duration of Second Injection, 1.25-mg Group

	Change from 6 Weeks to 9 Weeks		
	>11% Decrease (n = 7)	*Within ±11% (n = 9)*	*>11% Increase (n = 2)*
Change from 9 wks to 12 wks			
>11% decrease	0	1	0
Within ±11%	4	6	2
>11% increase	3	2	0

Change in central subfield thickness categorized according to whether it exceeded 11%, the reliability limit for real change determined in another Diabetic Retinopathy Clinical Research Network study.[20] Group B. N = 18 eyes with data at 6 wks, 9 wks, and 12 wks.

Table 8. Duration of Bevacizumab Effect Based on Change in Central Subfield Thickness: Duration of Second Injection, 2.5-mg Group

	Change from 6 Weeks to 9 Weeks		
	>11% Decrease (n = 3)	*Within ±11% (n = 17)*	*>11% Increase (n = 2)*
Change from 9 wks to 12 wks			
>11% decrease	0	2	1
Within ±11%	2	14	1
>11% increase	1	1	0

Change in central subfield thickness categorized according to whether it exceeded 11%, the reliability limit for real change determined in another Diabetic Retinopathy Clinical Research Network study.[20] Group C. N = 22 eyes with data at 6 wks, 9 wks, and 12 wks.

Table 9. Three-Week Outcomes in Bevacizumab Groups* According to Subject Characteristics

	Change in Central Subfield Thickness (μm) from Baseline to 3 Weeks			Change in Visual Acuity (Letters) from Baseline to 3 Weeks		
	n	*Median (Quartiles)*	P *Value*†	*n*	*Median (Quartiles)*	P *Value*†
Baseline central subfield thickness‡			<0.0001§			0.22
<400 μm	43	−3 (−49, +13)		44	+1 (−2, +8)	
≥400 μm	41	−102 (−145, −6)		43	+5 (0, +8)	
Baseline visual acuity‡			0.31			0.006‖
<65 letters	41	−35 (−130, +5)		44	+3 (0, +9)	
≥65 letters	43	−28 (−102, +13)		43	+1 (−3, +7)	
Age‡			0.44			0.23
≤66 yrs	41	−45 (−131, +5)		42	+4 (−1, +8)	
>66 yrs	43	−16 (−107, +6)		45	+2 (0, +8)	
Gender			0.55			0.37
Female	33	−28 (−115, +6)		33	+3 (0, +8)	
Male	51	−35 (−105, +5)		54	+3 (−1, +7)	
Prior treatment for DME			0.16			0.04
No	26	−40 (−141, −3)		26	+5 (−1, +8)	
Yes	58	−29 (−102, +7)		61	+2 (−1, +8)	
Baseline retinopathy severity¶			0.53			0.38
<Severe NPDR	52	−31 (−115, +6)		53	+3 (0, +8)	
PDR or severe NPDR	27	−31 (−105, +13)		29	+1 (−3, +7)	
Baseline clinical DME characterization#			0.93			0.45
Typical/predominantly focal	14	−13 (−67, −2)		14	+7 (0, +9)	
Neither predominantly focal nor diffuse	20	−8 (−32, +20)		21	0 (−5, +5)	
Typical/predominantly diffuse	50	−82 (−139, +5)		52	+3 (0, +8)	
Baseline subretinal fluid			0.52			0.06
Definite/questionable	21	−35 (−131, +24)		21	+6 (+3, +11)	
No evidence	63	−29 (−102, +3)		66	+1 (−1, +7)	

DME = diabetic macular edema; NPDR = nonproliferative diabetic retinopathy.
*Groups B–E pooled. Optical coherence tomography was not done at the 3-wk visit by 3 subjects.
†From least-squares regression model, adjusted by baseline score. Medians and interquartile ranges are reported rather than means and standard deviations because of the small sample size per group to present a better perspective on the distribution of the data and to minimize the effect of extreme values.
‡Continuous factor used for calculating *P* value.
§Median (quartiles) percent change in central subfield thickening at 3 wks: for baseline thickness < 400 μm, −2% (−37%, +9%); for baseline thickness ≥ 400 μm, −26% (−56%, −2%). *P* for continuous measure of baseline thickness from a least-squares regression model = 0.12.
‖Median (quartiles) percent reduction in visual acuity deficit at 3 wks: for baseline acuity < 65 letters, +11% (0%, +25%); for baseline acuity ≥ 65 letters, +7% (−12%, +33%). *P* for continuous measure of baseline acuity from a least-squares regression model = 0.40.
¶Excludes 5 missing baseline retinopathy severity (photographs lost or ruined for 3 subjects, could not grade for 2).
#*P* value for typical/predominantly focal versus typical/predominantly diffuse.

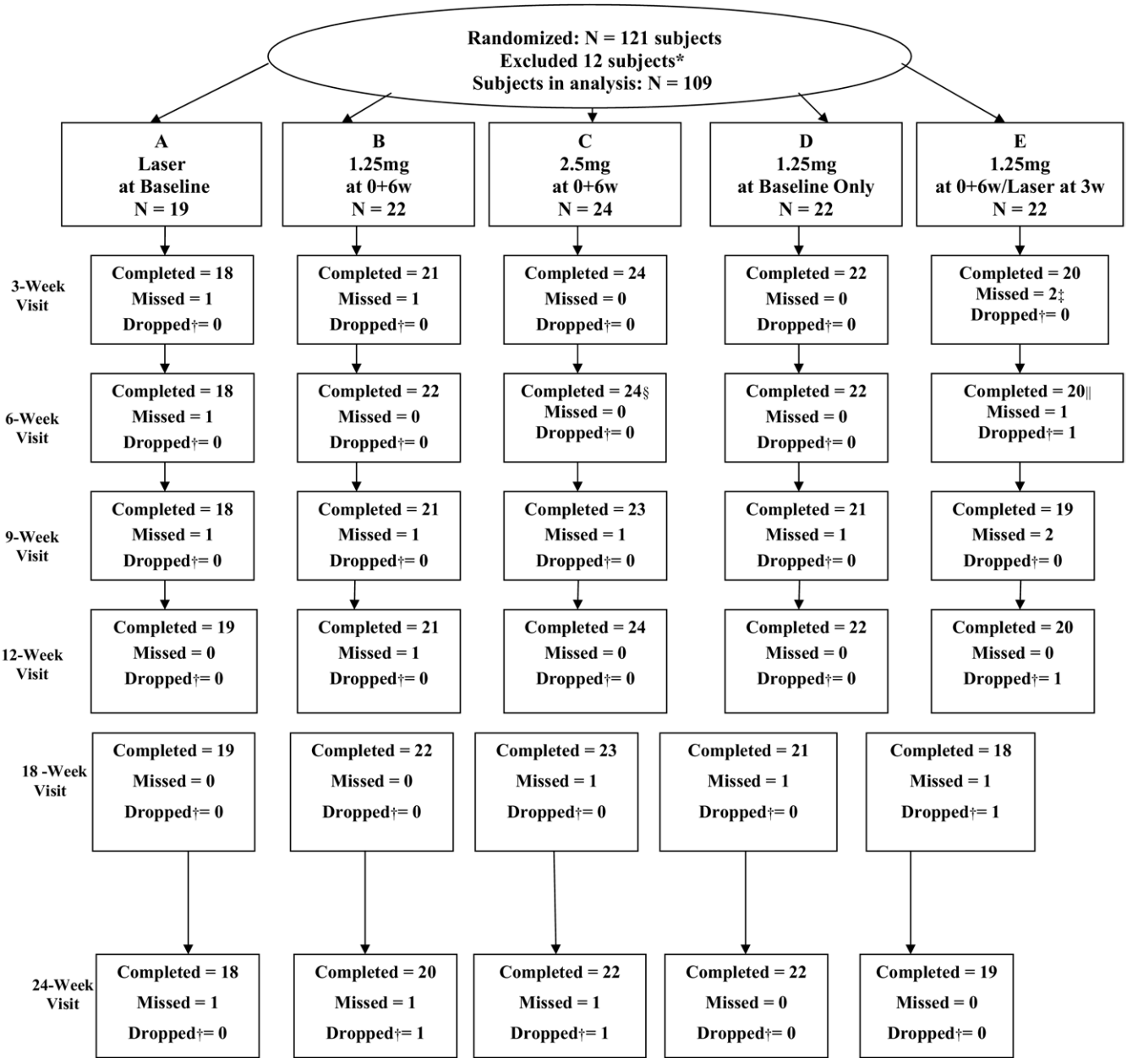

Figure 1. Subject outcome visit follow-up flowchart. w = weeks. *Nine subjects/eyes excluded due to ineligibility: 1 received laser treatment within 3 months before randomization; 5 had baseline central subfield thickness (CST) < 275 μm; 1 had a baseline optical coherence tomography image that could not be graded due to low signal strength and, therefore, was unable to have CST confirmed for eligibility; and 2 had choroidal neovascularization first identified by the Reading Center and subsequently confirmed by the enrolling ophthalmologist after randomization. Two subjects with no follow-up visits and 1 subject with endophthalmitis after the initial injection also were excluded. †Includes deaths, withdrawals, and loss to follow-up occurring since the last visit. ‡Laser given late at 6 weeks for one. §Injection missed for 2. ‖Injection given late at 9 weeks for one.