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Expanded 2-year Follow-up of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema

Diabetic Retinopathy Clinical Research Network*
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Abstract

Objective—To report expanded 2-year follow up of a previously reported randomized trial evaluating intravitreal 0.5-mg ranibizumab or 4-mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of diabetic macular edema (DME).

Design—Multicenter, randomized clinical trial.

Participants—Eight hundred and fifty four study eyes of 691 participants with visual acuity of 20/32 to 20/320 (approximate Snellen equivalent) and DME involving the fovea.

Methods—Continuation of procedures previously reported for the randomized trial.

Main Outcome Measures—Best-corrected visual acuity and safety at the 2-year visit.

Results—At the 2-year visit, compared with the sham plus prompt laser group, the mean change in the visual acuity letter score from baseline was 3.7 letters greater in the ranibizumab plus prompt laser group (95% confidence interval adjusted for multiple comparisons [aCI]: -0.4 to +7.7) l, 5.8 letters greater in the ranibizumab plus deferred laser group (95% aCI: +1.9 to +9.8) and 1.5 letters worse in the triamcinolone plus prompt laser group (95% aCI : -5.5 to +2.4). After

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*A published list of the Diabetic Retinopathy Clinical Research Network investigators and staff participating in this protocol can be found in *Appendix 1(*available at http://aaojournal.org).

Members of the DRCR.net who participated in this protocol are listed in appendix 1

the 1- through the 2-year visit in the ranibizumab with prompt or deferred laser groups, the median numbers of injections were 2 and 3 (potential maximum of 13), respectively. At the 2-year visit, the percentages of eyes with central subfield thickness ≥250 μm were 59% in the sham + prompt laser group, 43% in the ranibizumab + prompt laser group, 42% in the ranibizumab + deferred laser group, and 52% in the triamcinolone + prompt laser group. No systemic events attributable to study treatment were apparent. Three eyes in 3 (0.8%) of 375 participants had injection-related endophthalmitis in the ranibizumab groups while elevated intraocular pressure and cataract surgery were more frequent in the triamcinolone+prompt laser group.

Conclusions—The expanded 2-year results reported herein are similar to results published previously and reinforce the conclusions originally reported, that ranibizumab should be considered for patients with DME and characteristics similar to the cohort in this clinical trial, including vision impairment with DME involving the center of the macula.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a comparative effectiveness randomized clinical trial in 691 study participants (854 study eyes) to evaluate 3 different treatments, including intravitreal 0.5-mg ranibizumab combined with prompt or deferred (≥24 weeks) focal/grid laser or 4-mg triamcinolone combined with prompt focal/grid laser, compared with sham injections with prompt focal/grid laser alone for treatment of center-involved diabetic macular edema (DME).[1] The study found that intravitreal ranibizumab with prompt or deferred laser was more effective through at least 1 year compared with prompt laser alone for the treatment of DME involving the central macula, although uncommonly associated with endophthalmitis. In pseudophakic eyes, results with intravitreal triamcinolone plus prompt laser appeared similar to results in the ranibizumab arms and were more effective than laser alone but the triamcinolone plus prompt laser arm had an increased risk of intraocular pressure elevation.

Based on these results, the study was extended for each willing study participant from the preplanned 3 years to 5 years from randomization. Eyes originally assigned to ranibizumab plus prompt laser or ranibizumab plus deferred laser will continue to follow their original randomization protocol and the protocol's post 52-week treatment schedule and follow-up visit schedule through 5 years to gain insight into the long-term course of DME treated with ranibizumab in combination with prompt or deferred laser. Eyes originally assigned to sham plus prompt laser or triamcinolone plus prompt laser were given the opportunity to receive intravitreal ranibizumab following the same retreatment algorithm as was followed at baseline within the ranibizumab plus prompt laser group. When the primary (1-year) outcome results were reported,[1] 391 participants (57%) had reached the 2-year visit, and all data available through the 2-year visit were included in that publication. Between data set closure for the one year results and the manuscript publication (and the resultant change in study protocol), all study patients were followed according to the original study design. This report provides study data available through 2 years for safety outcomes and other data up to 2 years but prior to a time when a participant not originally assigned to ranibizumab could elect to switch to ranibizumab treatment within the protocol design.

Methods

The study procedures and statistical methods have been reported[1] and are not repeated herein. The study adhered to the tenets of the Declaration of Helsinki. The protocol and Health Insurance Portability and Accountability Act compliant informed consent forms were approved by multiple institutional review boards. The protocol is available on the DRCR.net website (www.drcr.net, date accessed November 4, 2010). In brief, the trial included 854 study eyes of 691 participants (mean age 63±10 years, 44% women) with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320 (median baseline visual acuity approximately 20/50) and DME involving the fovea (mean optical coherence tomography

(OCT) central subfield retinal thickness 405 μm). Sixty-three percent of the participants had received treatment for DME prior to enrollment, and 68% were phakic at baseline. Key baseline characteristics of the 4 treatment groups were similar for eyes that completed the 2-year visit (data not shown). There were no substantial differences identified in the baseline characteristics of those who completed and those who did not complete the 2-year visit (Table 1, available at http://aaojournal.org).

Two-year data prior to the protocol change being implemented were available for 642 eyes among 526 participants and were not available for 212 eyes (25%) among 165 participants (Figure 1, available at http://aaojournal.org) for the following reasons: deaths (35), withdrawals from the study (47), loss to follow-up (28), unavailable for the 2-year visit (3), the 2-year visit occurred after the protocol change was implemented, when all participants could receive ranibizumab (99). In addition, data from 1 clinical site in which a majority of eyes were judged not to meet the OCT eligibility criterion of central subfield ≥250μm when graded manually at a central reading center (14 eyes from 10 subjects) are excluded except for safety data. The primary outcome results are not different if these study participants are included. All safety data through the 2-year visit available as of November 8, 2010 are reported among these 526 participants plus the 165 participants whose 2-year visit occurred after the protocol change described above was implemented.

Results

Between the 1- and 2-year visits, in the ranibizumab with prompt or deferred laser arms the median numbers of injections were 2 and 3 out of a potential maximum of 13 while the median number of visits were 7 and 10 out of a potential maximum of 13, respectively. Most eyes assigned to ranibizumab received at least 1 injection due to recurrence of center-involved DME between the 1- and 2-year visits, even if success criteria had been attained (visual acuity Snellen equivalent 20/20 or better, or OCT central subfield <250μm) at the 1-year visit (Table 2). The percentages of eyes receiving at least 1 session of focal/grid laser in the ranibizumab+deferred laser group increased from 28% in the first year to 42% by the 2-year visit (Table 2). Between the 1- and 2-year visits 40% in the ranibizumab+prompt laser group and 29% in the ranibizumab+deferred laser group received at least 1 session of focal/grid laser. Between the 1- and 2-year visits, 51% of the eyes in the sham+prompt laser and 52% in the triamcinolone+ prompt laser group received one or more sessions of focal grid laser. In the triamcinolone+prompt laser group, 68% of eyes received at least one triamcinolone injection between the 1- and 2-year visits. An adverse event precluded a study drug injection in 0.4%, 0.5% and 2% of visits in the ranibizumab+prompt laser, ranibizumab +deferred laser, and triamcinolone+prompt laser groups, respectively through 2 years. Compliance with a sham or study drug injection was also excellent with 96%, 95%, 98%, and 96% in the sham+prompt laser, ranibizumab+prompt laser, ranibizumab+deferred laser, and triamcinolone+prompt laser groups, respectively receiving a sham or study drug injection when required by the protocol through 2 years.

Figure 2a shows the mean visual acuity change from baseline over time for the cohort of 642 eyes with 2-year follow-up data, which appears similar to the mean visual acuity change from baseline over time for all randomized study participants (Figure 3, available at http://aaojournal.org). At the 2-year visit, compared with the sham plus prompt laser group, the mean change in the visual acuity letter score from baseline was 3.7 (95% confidence interval adjusted for multiple comparisons [aCI]: -0.4 to +7.7) letters greater in the ranibizumab plus prompt laser group, 5.8 (95% aCI: +1.9 to +9.8) letters greater in the ranibizumab plus deferred laser group and 1.5 (95% aCI : -5.5 to +2.4) letter less in the triamcinolone plus prompt laser group (Table 3). These mean changes were associated with

a greater chance of substantial improvement and a smaller chance of substantial loss in visual acuity from baseline in eyes assigned to ranibizumab (Table 3).

Visual acuity outcomes at the 1-year visit largely appeared to be sustained through the 2-year visit in the ranibizumab arms (Table 4, available at http://aaojournal.org). However, the mean difference in visual acuity between the ranibizumab plus prompt laser group compared with sham plus prompt laser group was slightly smaller at 2 years compared with 1 year (3.7 versus 5.2 letters among eyes with data at both time points) while the mean difference in visual acuity between the ranibizumab+deferred laser group compared with sham+prompt laser group changed little at 2 years compared with 1 year (5.8 versus 6.1 letters among eyes with data at both time points). There was little vision improvement between the 1- and 2-year visits in the sham plus prompt laser group.

Among the eyes that were pseudophakic at baseline (Figure 4 and Tables 5 and 6, available at http://aaojournal.org), the mean change in the visual acuity letter score from baseline to the 2-year visit was 1.6 letters (95% aCI: -4.5 to +7.6) greater in the triamcinolone plus prompt laser group compared with the sham plus prompt laser group, and was similar to difference in outcomes between the ranibizumab plus prompt laser group (+0.5 letter, 95% aCI: -5.5, +6.6) and the ranibizumab plus deferred laser group (+3.5 letters, 95% aCI: -2.3, +9.3) compared with the sham plus prompt laser group.

OCT data mirrored the visual acuity data most closely in the ranibizumab groups (Figure 2b, Table 7, Table 8 [available at http://aaojournal.org], and Figure 5 [available at http://aaojournal.org]). At 2 years, the percentages of eyes with central subfield thickness 250 μm or greater were 59% in the sham + prompt laser group, 43% in the ranibizumab + prompt laser group 42% in the ranibizumab + deferred laser group, and 52% in the triamcinolone + prompt laser group; corresponding percentages of eyes with thickness ≥ 300 μm were 36%, 20%, 24%, and 27%. The ranibizumab groups and the triamcinolone plus prompt laser group appeared less likely than the sham plus prompt laser group to receive panretinal photocoagulation (PRP) (Table 9, available at http://aaojournal.org). No systemic events attributable to study treatment were apparent while major ocular adverse events during follow-up show little difference from results published previously (Table 10, available at http://aaojournal.org and Figure 6, available at http://aaojournal.org), with 3 eyes in 3 (0.8%) of 375 participants experiencing injection-related endophthalmitis in the ranibizumab groups while elevated intraocular pressure and cataract surgery remianed more frequent in the triamcinolone+prompt laser group.[1]

Discussion

The expanded 2-year results reported herein are similar to results published previously[1] and reinforce the conclusions originally reported, that ranibizumab with prompt or deferred focal/grid laser should be considered for patients with DME and characteristics similar to the cohort in this clinical trial, including vision impairment with DME involving the center of the macula. These outcomes are reinforced further by similar results in two recently published studies of intravitreal anti-VEGF treatment for DME, one using bevacizumab and one using ranibizumab.[2], [3] The superiority of both ranibizumab treatment groups over the sham plus prompt laser treatment group appears to be sustained through 2 years. Furthermore, the relatively few injections (median 2 or 3 in the ranibizumab plus prompt or deferred laser groups, respectively) coupled with the relatively stable visual acuity outcomes between the 1- and 2-year visits suggest that the DRCR.net retreatment algorithm was successful in avoiding vision loss while reducing the number of injections needed through 2 years. Nevertheless, approximately 40% of the eyes in the two ranibizumab groups still had central macular edema (OCT central subfield ≥250 μm) at the 2-year visit, although in only

20% to 24% was the retina more than mildly thickened (OCT central subfield ≥300 μm). Longer follow-up of this cohort will allow for the assessment of other differences between immediate and deferred laser in the ranibizumab treated groups. Eventual differences in the amount of laser treatment, amount of ranibizumab treatment and the number of visits necessary can eventually be assessed. The possible reasons for the potential difference in the number of visits in year 2 between the ranibizumab with prompt laser and ranibizumab with deferred laser groups (7 and 10 visits respectively) will be explored further in future reports.

Compared with the sham plus prompt laser group, the difference in mean visual acuity at the 2-year visit was nearly identical to the outcome at the 1-year visit in the ranibizumab plus deferred laser group, the mean difference in visual acuity in the ranibizumab plus prompt laser group was slightly smaller at the 2-year visit compared with the 1-year visit (3.7 versus 5.2 letters among eyes with data at both time points). The 95% aCI on the mean difference (-0.4, +7.7) included zero due to this slight narrowing of the treatment group difference as well as due to greater variability of the visual acuity scores at the 2-year compared with the 1-year visit (standard deviation 12 versus 13 and 13 versus 15 in the ranibizumab and sham groups respectively).

As reported previously, overall, intravitreal triamcinolone combined with focal/grid laser did not result in superior visual acuity outcomes compared with sham+prompt laser. Also as reported previously, in an analysis limited to pseudophakic eyes, the triamcinolone+prompt laser group's outcome for visual acuity was of similar magnitude to that of the two ranibizumab groups.

The methods of this study did not address the cost-effectiveness of this treatment or its impact on costs associated with vision impairment, and it is beyond the scope of this study to determine if other treatment algorithms (such as retreatment every 4 weeks through 2 years) or other anti-VEGF drugs (such as bevacizumab or aflibercept) would result in different or similar outcomes. The sustained decreased chance of PRP in the ranibizumab and triamcinolone groups merits further investigation to determine the role of anti-VEGF drugs in the prevention or treatment of proliferative diabetic retinopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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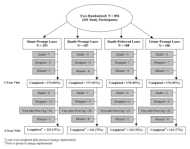


Figure 1. Completion of Follow-up for Study Eyes

One year completed visits include visits that occurred between 308 and 420 days (between 44 and 60 weeks) from randomization. Two year completed visits include visits that occurred between 616 and 840 days (between 88 and 120 weeks) from randomization. Ranib = Ranibizumab; Triam = Triamcinolone

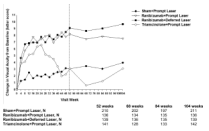


Figure 2a. Mean Change in Visual Acuity at Follow-up Visits for Cohort that Completed 2-Year Visit

Values that were ±30 letters were assigned a value of 30. *P* values for difference in mean change in visual acuity from sham+prompt laser at the 104-week study visit: ranibizumab +prompt laser =0.03, ranibizumab+deferred laser <0.001, and triamcinolone+prompt laser groups = 0.35. Each visit week includes visits that are ±14 days, except at the 52-week visit which includes visits that occur between 308 and 420 days (between 44 and 60 weeks) from randomization and at the 104-week visit which includes visits that occur between 616 and 840 days (between 88 and 120 weeks) from randomization.

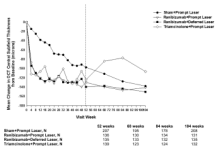


Figure 2b. Mean Change in Optical Coherence Tomography Central Subfield Retinal Thickening at Follow-up Visits for Cohort that Completed 2-Year Visit

P values for difference in mean change in optical coherence tomography (OCT) central subfield retinal thickness from sham+prompt laser at the 104-week visit: ranibizumab +prompt laser = 0.003, ranibizumab+deferred laser = 0.01, and triamcinolone+prompt laser = 0.37. Each visit week includes visits that are ±14 days, except at the 52-week visit which includes visits that occur between 308 and 420 days (between 44 and 60 weeks) from randomization and at the 104-week visit which includes visits that occur between 616 and 840 days (between 88 and 120 weeks) from randomization.

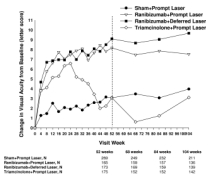


Figure 3. Mean Change in Visual Acuity at Follow-up Visits Using All Available Data

Values that were ±30 letters were assigned a value of 30. *P* values for difference in mean change in visual acuity from sham+prompt laser at the 104-week study visit: ranibizumab +prompt laser = 0.05, ranibizumab+deferred laser <0.001, and triamcinolone+prompt laser groups = 0.57. Each visit week includes visits that are ±14 days, except at the 52-week visit which includes visits that occur between 308 and 420 days (between 44 and 60 weeks) from randomization and at the 104-week visit which includes visits that occur between 616 and 840 days (between 88 and 120 weeks) from randomization.

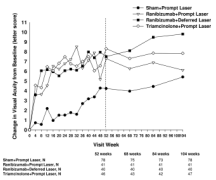
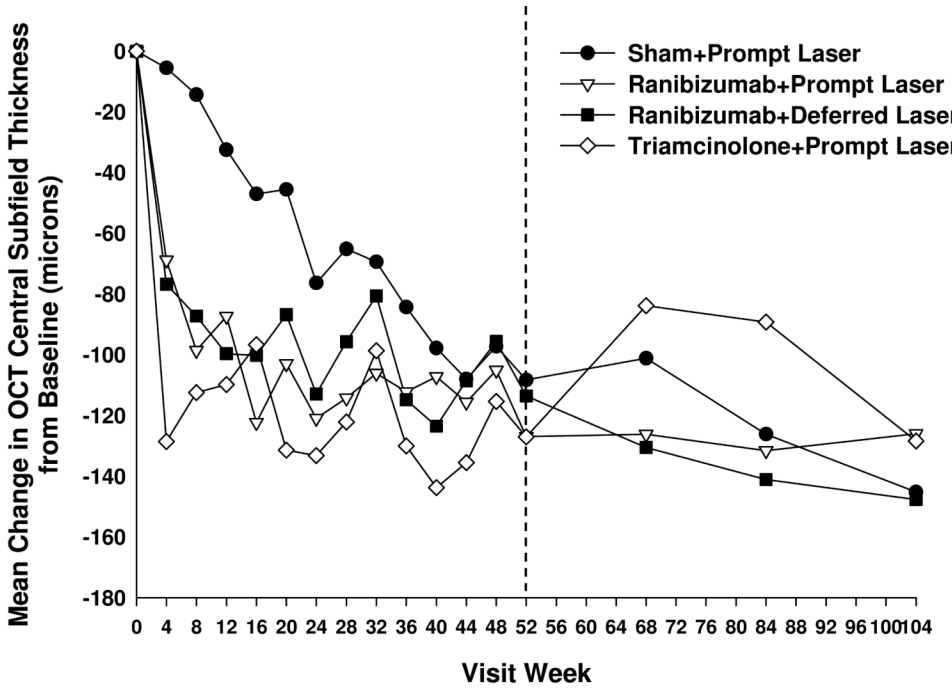


Figure 4. Mean Change in Visual Acuity at Follow-up Visits among Eyes that were Pseudophakic at Baseline for Cohort that Completed 2-Year Visit

Values that were ±30 letters were assigned a value of 30. *P* values for difference in mean change in visual acuity from sham+prompt laser at the 104-week study visit: ranibizumab +prompt laser =0.83, ranibizumab+deferred laser = 0.15, and triamcinolone+prompt laser groups = 0.53. Each visit week includes visits that are ±14 days, except at the 52-week visit which includes visits that occur between 308 and 420 days (between 44 and 60 weeks) from randomization and at the 104-week visit which includes visits that occur between 616 and 840 days (between 88 and 120 weeks) from randomization.



	52 weeks	68 weeks	84 weeks	104 weeks
Sham+Prompt Laser, N	76	73	67	77
Ranibizumab+Prompt Laser, N	41	38	40	40
Ranibizumab+Deferred Laser, N	39	39	39	38
Triamcinolone+Prompt Laser, N	46	42	42	45

Figure 5. Mean Change in Optical Coherence Tomography Central Subfield Retinal Thickening at Follow-up Visits for Eyes that Were Pseudophakic at Baseline for Cohort that Completed 2-Year Visit

P values for difference in mean change in optical coherence tomography (OCT) central subfield retinal thickness from sham+prompt laser at the 104-week visit: ranibizumab +prompt laser = 0.32, ranibizumab+deferred laser =0.68, and triamcinolone+prompt laser = 0.44. Each visit week includes visits that are ±14 days, except at the 52-week visit which includes visits that occur between 308 and 420 days (between 44 and 60 weeks) from randomization and at the 104-week visit which includes visits that occur between 616 and 840 days (between 88 and 120 weeks) from randomization.

OCT = optical coherence tomography.

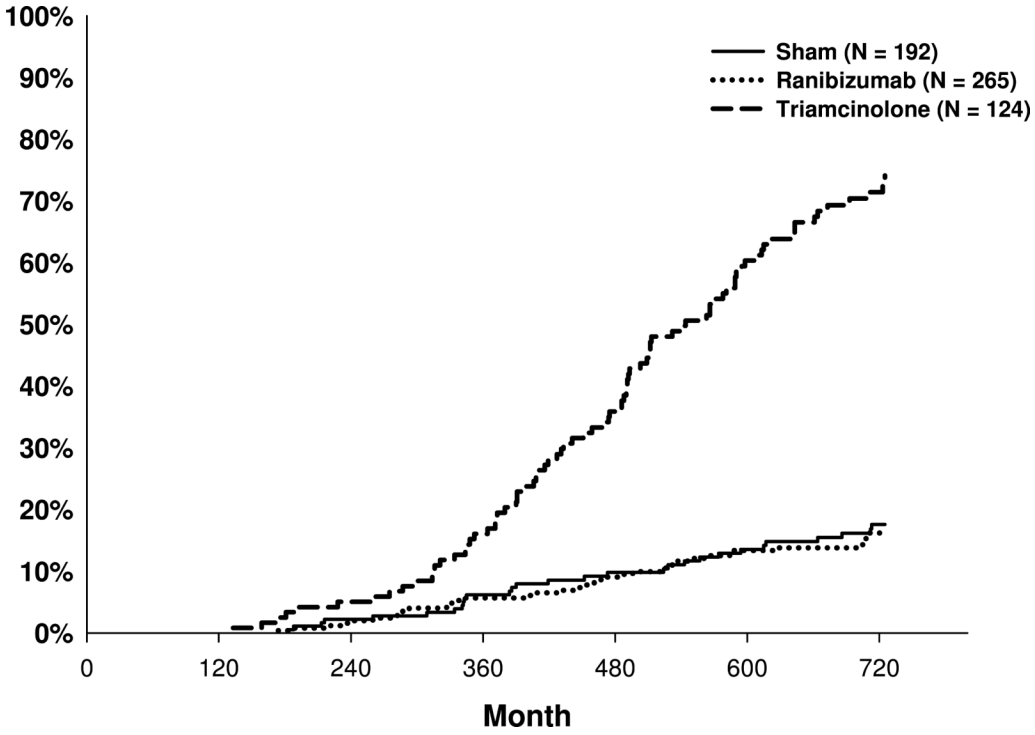


Figure 6. Cumulative Probability of Cataract Surgery through the 2-Year Study Visit for All Eyes Phakic at Baseline

Eyes pending a 2-year visit or who were lost to follow-up were censored at their last visit. N is the number of eyes phakic at baseline.

Table 1

Baseline Characteristics Comparing Completers and Non-completers*

	Completers N = 628 eyes	Non-completers† N = 200 eyes
Treatment Group - N (%)		
Sham	211 (34%)	73 (37%)
Ranibizumab	275 (44%)	86 (43%)
Triamcinolone	142 (23%)	41 (21%)
Gender: Women - N (%)	273 (43%)	83 (42%)
Age (years) - median (25^{th}, 75^{th} percentile)	63 (57, 70)	63 (55, 71)
Race - N (%)		
White	464 (74%)	136 (68%)
African American	97 (15%)	41 (21%)
Hispanic or Latino	54 (9%)	16 (8%)
Asian	8 (1%)	3 (2%)
Native Hawaiian/Other Pacific Islander	1 (<1%)	0
American Indian/Alaskan Native	0	0
More than one race	2 (<1%)	1 (1%)
Unknown/not reported	2 (<1%)	3 (2%)
Diabetes Type – N (%)		
Type 1	53 (8%)	12 (6%)
Type 2	563 (90%)	180 (90%)
Uncertain	12 (2%)	8 (4%)
Duration of Diabetes (years) - median (25^{th}, 75^{th} percentile)	17 (10, 24)	16 (11, 21)
HbAlc (%) - median (25^{th}, 75^{th} percentile)	7.3 (6.5, 8.4)	7.3 (6.6, 8.4)
Prior Panretinal Scatter Photocoagulation - N (%)	132 (21%)	29 (15%)
Prior Photocoagulation for DME - N (%)	375 (60%)	115 (58%)
IOP (mmHg) - median (25^{th}, 75^{th} percentile)	16 (14, 18)	16 (14, 18)
Lens Status Phakic (clinical exam) - N (%)	422 (67%)	133 (67%)
E-ETDRS Visual Acuity (letter score) - median (25^{th}, 75^{th} percentile)	66 (57, 73)	62 (56, 72)
Central Subfield Thickness (μm) on OCT‡ - median (25^{th}, 75^{th} percentile)	382 (314, 486)	398 (298, 492)
Retinal Volume (mm^3) on OCT‡ - median (25^{th}, 75^{th} percentile)	8.4 (7.6, 9.6)	8.7 (7.7, 10.3)
Retinopathy Severity Level (ETDRS Severity Scale)‡ - N (%)		
No DR/MA/Mild/Moderate NPDR	140 (23%)	47 (25%)
Moderately Severe/Severe NPDR	260 (43%)	91 (48%)
Mild/Moderate/High-risk PDR	202 (34%)	52 (27%)

HbAlc = hemoglobin Alc; DME = diabetic macular edema; E-ETDRS© = electronic Early Treatment Diabetic Retinopathy Study; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; OCT = optical coherence tomography; DR = diabetic retinopathy; MA = microaneurysms; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

*Excludes 14 eyes and 12 eyes, respectively, for completers and non-completers, from one clinical site in which a majority of eyes were judged not to meet the OCT eligibility criterion of central subfield ≥250μm when graded manually at a central reading center.

†Includes deaths (35), withdrawals from the study (39), loss to follow-up (24), unavailable for the 2-year visit (3), the 2-year visit after a time when all participants could receive ranibizumab (99).

[‡]Missing (or ungradable) OCT and fundus photograph data as follows for the completer and non-completers, respectively: central subfield (1, 0), retinal volume (133, 55), and retinopathy severity (13, 6).

Table 2

Treatments and Visits Prior to 2-Year Visit*

	Ranibizumab +Prompt Laser N = 136	Ranibizumab +Deferred Laser N = 139	Triamcinolone +Prompt Laser N = 141
Median (25th, 75th quartile) number of study visits and treatment assessment visits† from 1-year to (prior to) 2-year visit ‡	7 (5, 10)	10 (6, 12)	4 (4, 4)
Maximal possible number of study drug injections prior to 2-year visit	26	26	8
Median (25th, 75th quartile) number of study drug injections from baseline to (prior to) 1-year visit	8 (7, 11)	9 (7, 11)	3 (2, 4)
Median (25th, 75th quartile) number of study drug injections from 1-year to (prior to) 2-year visit	2 (0, 4)	3 (1, 7)	1 (0, 2)
Maximal possible number of focal/grid laser treatments prior to 2-year visit	8	6	8
Median (25th, 75th quartile) number of focal/grid laser treatments from baseline to (prior to) 1-year visit	2 (1, 3)	0 (0, 1)	2 (1, 3)
Median (25th, 75th quartile) number of focal/grid laser treatments from 1-year to (prior to) 2-year visit	0 (0, 1)	0 (0, 1)	1 (0, 1)
Number (%) of eyes that met success at 16 weeks and then received injection by 1-year visit	58 (87%) of 67	46 (84%) of 55	47 (85%) of 55
Number (%) of eyes that met success at 1-year visit and then received injection by 2-year visit	47 (56%) of 84	41 (59%) of 69	43 (56%) of 77

*Includes study participants completing the 2-year (104-week) visit.

†Only includes unscheduled visits for re-treatment assessment.

‡Median (25th, 75th quartile) numbers of all visits including study visits and unscheduled visits for any reason including retreatment assessment, adverse event, or post-op monitoring from 1-year to (prior to) 2-year visit are 8 (5, 11), 10 (6, 12), and 4 (4, 5) in ranibizumab+ prompt laser, ranibizumab+deferred laser, and triamcinolone+ prompt laser groups, respectively.

Table 3

Visual Acuity Outcomes from Baseline to 2-Year Visit*

	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 211	**N = 136**	**N = 139**	**N = 142**
Change in visual acuity (letter score)				
Mean±SD	+3 ± 15	+7 ± 13	+9 ± 14	+2 ± 19
Median (25th, 75th percentile)	+6 (-2, +12)	+8 (+2, +15)	+9 (+4, +16)	+6 (-4, +14)
Difference in mean change from sham+prompt laser (95% CI) [*P* value]†		+3.7 (-0.4,+7.7) [*P*=0.03]	+5.8 (+1.9,+9.8) [*P*<0.001]	-1.5 (-5.5, +2.4) [*P* = 0.35]
Distribution of change, no. (%)				
≥15 letter improvement	37 (18%)	39 (29%)	39 (28%)	31 (22%)
14-10 letter improvement	38 (18%)	21 (15%)	29 (21%)	27 (19%)
9-5 letter improvement	42 (20%)	32 (24%)	30 (22%)	16 (11%)
Same ±4 letters	50 (24%)	26 (19%)	34 (24%)	33 (23%)
5-9 letters worse	17 (8%)	8 (6%)	3 (2%)	8 (6%)
10-14 letters worse	6 (3%)	4 (3%)	1 (1%)	8 (6%)
≥15 letters worse	21 (10%)	6 (4%)	3 (2%)	19 (13%)
Difference in proportion with ≥10 letter improvement from sham +prompt laser (95% CI)‡		+8% (-4%, 21%)	+13% (+0.5%, +26%)	+6% (-7%, +18%)
Relative risk (95% CI) [P value]† for comparison with sham+ prompt laser	1.0	1.20 (0.87, 1.64) [*P*=0.17]	1.36 (1.02, 1.80) [*P*=0.01]	1.18 (0.87,1.60) [*P* = 0.19]
Difference in proportion with ≥10 letter worsening from sham+ prompt laser (95% CI)‡		-5% (-13%, -2%)	-10% (-16%, -3%)	+6% (-3%, +16%)
Relative risk (95% CI) [P value]† for comparison with sham+ prompt laser	1.0	0.58 (0.25, 1.35) [*P*=0.12]	0.23 (0.06, 0.80) [*P* = 0.005]	1.48 (0.83, 2.63) [*P* = 0.10]
Difference in proportion with ≥15 letter improvement from sham+ prompt laser (95% CI)‡		+11% (-0.1%, +22%)	+11% (-0.5%, +22%)	+4% (-6%, +15%)
Relative risk (95% CI) [P value]† for comparison with sham+ prompt laser	1.0	1.53 (0.95, 2.46) [*P*=0.03]	1.61 (1.02, 2.54) [*P*=0.01]	1.31 (0.81, 2.13) [*P* = 0.18]
Difference in proportion with ≥15 letter worsening from sham+ prompt laser (95% CI)‡		-6% (-12%, +1%)	-8% (-14%, -2%)	+3% (-5%, +12%)
Relative risk (95% CI) [*P* value]† for comparison with sham+ prompt laser	1.0	0.45 (0.15, 1.32) [*P* = 0.08]	0.22 (0.05, 0.94) [*P* = 0.01]	1.33 (0.65, 2.72) [*P* = 0.34]

SD = standard deviation; CI = confidence interval.

[*] Includes only eyes with visual acuity measurements at baseline and 2-year visit. Visits occurring between 616 and 840 days (between 88 and 120 weeks) from randomization were included as 2-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used.

[†] Adjusted for baseline visual acuity and correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

[‡] Adjusted for correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

Table 4

Distribution of Visual Acuity at 1- and 2-Year Study Visits for the Cohort that Completed the 2-Year Visit*

	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 211	**N = 136**	**N = 139**	**N = 142**
Baseline visual acuity (letter score)				
Mean±SD	63 ± 12	63 ± 13	63 ± 11	64 ± 11
Median (25th, 75th percentile)	66 (56, 73)	66 (55, 73)	65 (56, 72)	66 (58, 72)
Change in visual acuity at the 1-year visit† (letter score)				
Mean±SD	+3 ± 13	+8 ± 12	+9 ± 11	+3 ± 12
Median (25th, 75th percentile)	+5 (-2, +11)	+9 (+2, +16)	+8 (+5, +15)	+4 (-4, +11)
Difference in mean change from sham +prompt laser (95% CI [P value] §		+5.2 (+2.1,+8.2) [*P*<0.001]	+6.1 (+3.1,+9.2) [*P*<0.001]	+0.6 (-2.4, +3.7) [*P* = 0.61]
Change in visual acuity at the 2-year visit‡ (letter score)				
Mean±SD	+3 ± 15	+7 ± 13	+9 ± 14	+2 ± 19
Median (25th, 75th percentile)	+6 (-2, +12)	+8 (+2, +15)	+9 (+4, +16)	+6 (-4, +14)
Difference in mean change from sham +prompt laser (95% CI) [*P* value]§		+3.7 (-0.4,+7.7) [*P*=0.03]	+5.8 (+1.9,+9.8) [*P*<0.001]	-1.5 (-5.5, +2.4) [*P* = 0.35]

*Includes only eyes with visual acuity measurements at baseline and 2-year visit.

†Visits occurring between 308 and 420 days (between 44 and 60 weeks) from randomization were included as 1-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 1-year target date were used. For the 2 eyes (1 in the sham+prompt laser group and 1 in the triamcinolone+prompt laser group) without any 1-year visit data, the last observation carried forward method was used to impute data for the 1-year analysis.

§Adjusted for baseline visual acuity and correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

[‡]Visits occurring between 616 and 840 days (between 88 and 120 weeks) from randomization were included as 2-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used.

Table 5

Visual Acuity Outcomes from Baseline to 2-Year Visits in Eyes that Were Pseudophakic at Baseline

	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 78	**N = 41**	**N = 40**	**N = 47**
Change in visual acuity (letter score)				
Mean±SD	+5 ± 15	+5 ± 17	+9 ± 17	+8 ± 13
Median (25th, 75th percentile)	+6 (-2, +14)	+7 (0, +15)	+9 (+4, +16)	+7 (+1, +14)
Difference in mean change from sham+prompt laser (95% CI) [*P* value]†		+0.5 (-5.5,+6.6) [*P*=0.83]	+3.5 (-2.3,+9.3) [*P*=0.15]	+1.6 (-4.5, +7.6) [*P* = 0.53]
Distribution of change, no. (%)				
≥15 letter improvement	16 (21%)	11 (27%)	12 (30%)	11 (23%)
14-10 letter improvement	13 (17%)	6 (15%)	7 (18%)	12 (26%)
9-5 letter improvement	15 (19%)	9 (22%)	7 (18%)	5 (11%)
Same ±4 letters	21 (27%)	8 (20%)	12 (30%)	14 (30%)
5-9 letters worse	6 (8%)	3 (7%)	1 (3%)	1 (2%)
10-14 letters worse	2 (3%)	2 (5%)	0	2 (4%)
≥15 letters worse	5 (6%)	2 (5%)	1 (3%)	2 (4%)
Difference in proportion with ≥10 letter improvement from sham +prompt laser (95% CI)‡		+5% (-18%, +28%)	+11% (-11%, +33%)	+12% (-10%, +34%)
Relative risk (95% CI) [P value]† for comparison with sham+ prompt laser	1.0	1.09 (0.61, 1.96) [*P*=0.72]	1.23 (0.77, 1.95) [*P*=0.29]	1.28 (0.79, 2.09) [*P* = 0.22]
Difference in proportion with ≥10 letter worsening from sham+ prompt laser (95% CI)‡		+0.8% (-13%, +14%)	-6% (-16%, +3%)	+0.5% (-13%, +12%)
Relative risk (95% CI) [P value]† for comparison with sham+ prompt laser	1.0	1.09 (0.27, 4.33) [*P*=0.88]	0.28 (0.02, 3.30) [*P* = 0.22]	0.95 (0.23, 3.97) [*P* = 0.93]
Difference in proportion with ≥15 letter improvement from sham+ prompt laser (95% CI)‡		+6% (-14%, +26%)	+9% (-11%, +30%)	+3% (-15%, +21%)
Relative risk (95% CI) [P value]† for comparison with sham+ prompt laser	1.0	1.20 (0.54, 2.71) [*P*=0.58]	1.37 (0.64, 2.94) [*P*=0.32]	1.09 (0.50, 2.40) [*P* = 0.79]
Difference in proportion with ≥15 letter worsening from sham+ prompt laser (95% CI)‡		-2% (-12%, +9%)	-4% (-13%, +5%)	-2% (-12%, +7%)
Relative risk (95% CI) [*P* value]† for comparison with sham+ prompt laser	1.0	0.76 (0.12, 4.98) [*P* = 0.73]	0.40 (0.03, 4.90) [*P* = 0.38]	0.66 (0.10, 4.49) [*P* = 0.60]

SD = standard deviation; CI = confidence interval.

* Includes only eyes with visual acuity measurements at baseline and 2-year visit. Visits occurring between 616 and 840 days (between 88 and 120 weeks) from randomization were included as 2-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used.

† Adjusted for baseline visual acuity and correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

‡ Adjusted for correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

Table 6

Distribution of Visual Acuity at 1- and 2- Year Study Visits in Eyes that Were Pseudophakic at Baseline for the Cohort that Completed the 2-Year Visit*

Change in visual acuity letter score	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 78	**N = 41**	**N = 40**	**N = 47**
Baseline visual acuity (letter score)				
Mean±SD	62 ± 13	61 ± 14	59 ± 12	60 ± 12
Median (25th, 75th percentile)	65 (54, 72)	65 (53, 73)	61 (50, 70)	63 (53, 70)
Change in visual acuity at the 1-year visit† (letter score)				
Mean±SD	+4 ± 15	+7 ± 14	+8 ± 10	+9 ± 10
Median (25th, 75th percentile)	+6 (-2, +11)	+7 (+4, +13)	+6 (+2, +13)	+9 (+4, +16)
Difference in mean change from sham +prompt laser (95% CI) [P value]§		+3.3 (-2.0,+8.6) [*P*=0.14]	+3.3 (-2.0,+8.6) [*P*=0.14]	+4.9 (-0.3, +10.0) [*P* = 0.02]
Change in visual acuity at the 2-year visit‡ (letter score)				
Mean±SD	+5 ± 15	+5 ± 17	+9 ± 17	+8 ± 13
Median (25th, 75th percentile)	+6 (-2, +14)	+7 (0, +15)	+9 (+4, +16)	+7 (+1, +14)
Difference in mean change from sham +prompt laser (95% CI) [*P* value]§		+0.5 (-5.5,+6.6) [*P*=0.83]	+3.5 (-2.3,+9.3) [*P*=0.15]	+1.6 (-4.5, +7.6) [*P* = 0.53]

CI=Confidence Interval, SD=Standard Deviation

* Includes only eyes with visual acuity measurements at baseline and 2-year visit.

† Visits occurring between 308 and 420 days (between 44 and 60 weeks) from randomization were included as 1-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 1-year target date were used. For 1 eye in the triamcinolone+prompt laser group without any 1-year data, the last observation carried forward method was used to impute data for the 1-year analysis.

[§] Adjusted for baseline visual acuity and correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

[‡] Visits occurring between 616 and 840 days (between 88 and 120 weeks) from randomization were included as 2-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used.

Table 7

Change in Retinal Thickness from Baseline to 2-Year Study Visit*

OCT Central Subfield Thickness	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 211	**N = 136**	**N = 139**	**N = 142**
Overall Change				
Thickness (μm) median (25th, 75th percentile)	266 (203, 350)	239 (197, 281)	231 (203, 299)	251 (207, 304)
Change from baseline (μm) Mean±SD†	-138±149	-141±155	-150±143	-107±145
Change from baseline (μm) median (25th, 75th percentile)	-113 (-234,-27)	-113 (-229, -43)	-129 (-216, -55)	-96 (-195, -24)
Difference in mean change from sham +prompt laser (95% CI) [*P* value]‡		-31 (-56, -6) [*P* = 0.003]	-28 (-53, -3) [*P* = 0.01]	-10 (-35, +16) [*P* = 0.37]
***Thickness <250 with at least a 25 μm decrease from baseline** , no. (%)*	81 (39%)	71 (54%)	75 (56%)	60 (45%)
Relative risk (95% CI) [*P* value]§ for comparison with sham+prompt laser		1.34 (1.03, 1.76) [*P* = 0.01]	1.35 (1.03, 1.78) [*P* = 0.01]	1.16 (0.88, 1.52) [*P* = 0.21]

OCT Retinal Volume†	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 182	**N = 121**	**N = 114**	**N = 119**
Total volume (mm^3) at 2 year				
Mean±SD	7.8±1.4	7.3±1.2	7.3±1.2	7.6±1.5
Median (25th, 75th percentile)	7.5 (6.9, 8.3)	7.1 (6.6, 7.6)	7.1 (6.6, 7.7)	7.3 (6.8, 8.2)
Change in volume (mm^3) from baseline □				
Mean±SD	-1.2±1.4	-1.5±1.5	-1.6±1.8	-1.2±1.7
Median (25th, 75th percentile)	-0.9 (-1.8, -0.4)	-1.2 (-2.2, -0.7)	-1.1 (-2.1, -0.5)	-1.2 (-2.1, -0.4)
Difference in mean change from sham +prompt laser (95% CI) [P value]‡		-0.52 (-0.86, -0.18) [*P*<0.001]	-0.38 (-0.72, -0.05) [*P*=0.01]	-0.18 (-0.52, +0.16) [*P*=0.19]

OCT = optical coherence tomography; SD = standard deviation; CI = confidence interval.

[*] Includes only eyes with OCT measurements at baseline and 2-year study visits, visits occurring between 616 and 840 days (between 88 and 120 weeks) from randomization were included as 2-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used.

[†] Missing (or ungradable) data as follows for the sham+prompt laser, ranibizumab+prompt laser, ranibizumab+deferred laser, and triamcinolone +prompt laser groups, respectively: 3, 5, 4, 10.

[‡] Adjusted for baseline visual acuity, baseline CSF, and correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

[§] Adjusted for correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

[□] Missing (or ungradable) data as follows for the sham+prompt laser, ranibizumab+prompt laser, ranibizumab+deferred laser, and triamcinolone +prompt laser groups, respectively: 60, 45, 43, 45.

Table 8

Change in Retinal Thickness from Baseline to the 2-Year Study Visit* in Eyes that Were Pseudophakic at Baseline

OCT Central Subfield Thickness	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 78	N = 41	N = 40	N = 47
Overall Change				
Thickness (μm) median (25th, 75th percentile)	255 (198, 331)	220 (194, 270)	243 (211, 302)	245 (198, 294)
Change from baseline (μm) mean±SD†	-145±141	-126+162	-148+127	-128+137
Change from baseline (μm) median (25th, 75th percentile)	-118 (-247,-37)	-112 (-203, -52)	-130 (-213, -48)	-104 (-199, -40)
Difference in mean change from sham +prompt laser (95% CI) [*P* value]‡		-17 (-58, +24) [*P* = 0.32]	-7 (-47, +33) [*P* = 0.68]	-13 (-54, +28) [*P* = 0.44]
Thickness <250 with at least a 25 μm decrease from baseline, no. (%)	32 (42%)	27 (68%)	19 (50%)	23 (51%)
Relative risk (95% CI) [*P* Value]§ for comparison with sham+prompt laser		1.46 (0.95, 2.23) [*P* = 0.03]	1.06 (0.65, 1.74) [*P* = 0.78]	1.16 (0.75, 1.79) [*P* = 0.41]

OCT Retinal Volume†	Sham +Prompt Laser	Ranibizumab +Prompt Laser	Ranibizumab +Deferred Laser	Triamcinolone +Prompt Laser
	N = 78	N = 41	N = 40	N = 47
Total volume (mm^3) at 2-year study visit				
Mean±SD	7.6±1.1	7.1±1.3	7.3±1.1	7.3±0.8
Median (25th, 75th percentile)	7.3 (6.9, 8.1)	6.8 (6.2, 7.3)	7.0 (6.7, 7.8)	7.2 (6.8, 7.7)
Change in volume (mm^3) from baseline //				
Mean±SD	-1.3±1.4	-1.4±1.3	-1.6±1.7	-1.3±1.0
Median (25th, 75th percentile)	-1.0 (-2.0, -0.3)	-1.0 (-2.0, -0.6)	-1.1 (-1.9, -0.7)	-1.0 (-1.9, -0.5)
Difference in mean change from sham +prompt laser (95% CI) [*P* value]‡		-0.53 (-0.98, -0.07) [*P*=0.01]	-0.19 (-0.63, +0.25) [*P*=0.30]	-0.14 (-0.59, +0.31) [*P*=0.45]

OCT = optical coherence tomography; SD = standard deviation; CI = confidence interval.

[*] Includes only eyes with OCT measurements at baseline and 2-year study visits, visits occurring between 616 and 840 days (between 88 and 120 weeks) from randomization were included as 2-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used.

[†] Missing (or ungradable) data as follows for the sham+prompt laser, ranibizumab+prompt laser, ranibizumab+deferred laser, and triamcinolone +prompt laser groups, respectively: 1, 1, 2, 2.

[‡] Adjusted for baseline visual acuity, baseline retinal volume, and correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

[§] Adjusted for correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

[//] Missing (or ungradable) data as follows for the sham+prompt laser, ranibizumab+prompt laser, ranibizumab+deferred laser, and triamcinolone +prompt laser groups, respectively: 21,11,11,16.

Table 9

Panretinal Photocoagulation or Vitrectomy from Baseline to 2-Year Visit and from 1- to 2-Year Visit by Baseline Retinopathy Severity Group

	Sham N = 211	Ranibizumab N = 275	Triamcinolone N = 142
Eyes Receiving PRP or Vitrectomy from Baseline to 2-Year Visit*			
Baseline severity: Moderately severe NPDR or better, No. (%)	**N = 123**	**N = 155**	**N = 72**
PRP	6 (5%)	4 (3%)	3 (4%)
Vitrectomy	6 (5%)	5 (3%)	2 (3%)
Baseline severity: Severe NPDR or worse, No. (%)	**N = 77**	**N = 108**	**N = 67**
PRP	17 (22%)	5 (5%)	7 (10%)
Vitrectomy	6 (8%)	5 (5%)	1 (1%)

Eyes Receiving PRP or Vitrectomy from 1-Year to 2-Year Visit*			
Baseline severity: Moderately severe NPDR or better, No. (%)	**N = 123**	**N = 155**	**N = 72**
PRP	6 (5%)	3 (2%)	2 (3%)
Vitrectomy	6 (5%)	4 (3%)	2 (3%)
Baseline severity: Severe NPDR or worse, No. (%)	**N = 77**	**N = 108**	**N = 67**
PRP	10 (13%)	3 (3%)	6 (9%)
Vitrectomy	4 (5%)	4 (4%)	1 (1%)

NPDR = non-proliferative diabetic retinopathy, PRP=Panretinal photocoagulation.

* Includes study participants completing the 2-year (104-week) visit baseline retinopathy severity missing or ungradable for 11, 12, and 3 eyes in the sham+prompt laser, ranibizumab+prompt/deffered laser, and triamcinolone+prompt laser groups, respectively.

Table 10

Adverse Events during 2-Year Follow-up

Major ocular adverse events during follow-up	Sham +Prompt Laser† N = 293	Ranibizumab +Prompt Laser N = 187	Ranibizumab +Deferred Laser N = 188	Triamcinolone +Prompt Laser† N = 186
Number of ranibizumab injections	91	1759	2046	53
Number of triamcinolone injections	0	-	-	646
Endophthalmitis*, no. (% study participants / % injections)	1 (0.3% / 0.6%)	2 (1% / 0.1%)	2 (1% / 0.08%)	0
Pseudoendophthalmitis, no. (%)	1 (<1%)	0	0	1 (1%)
Ocular vascular event, no. (%)	2 (1%)	2 (1%)	1 (1%)	3 (2%)
Retinal detachment, no. (%)	1 (<1%)	0	1 (1%)	0

Cardiovascular events according to Antiplatelet Trialists' Collaboration**	Sham[a] N‡ = 130	Ranibizumab[b] N‡ = 375	Triamcinolone[c] N‡ = 186
Non-fatal myocardial infarction, no. (%)	4 (3%)	5 (1%)	5 (3%)
Non-fatal cerebrovascular accident – ischemic or hemorrhagic (or unknown), no. (%)	8 (6%)	7 (2%)	4 (2%)
Vascular death (from any potential vascular or unknown cause§), no. (%)	8 (6%)	13 (3%)	8 (4%)
Any ATC cardiovascular event, no. (%)	17 (13%)	25 (7%)	15 (8%)

ATC= Antiplatelet Trialists' Collaboration

*One case unrelated to study drug injection (following cataract extraction) in the sham+prompt laser group; 1 case related to study drug injection and 1 case unrelated to injection (following cataract surgery) in the ranibizumab+prompt laser group; 2 cases related to study drug injection in the ranibizumab+deferred laser group. The 3 cases related to study drug injection in the ranibizumab groups are 0.08% of ranibizumab study drug injections given. Endophthalmitis was defined as any patient having an intravitreal or anterior chamber tap for presumed endophthalmitis or treated for infectious endophthalmitis regardless of whether a tap was performed or whether a culture is positive.

†No major ocular adverse events for eyes with ranibizumab injections.

**Antiplatelet Trialists' Collaboration. BMJ. 1994 Jan 8;308(6921):81-106.

[a]One participant had a nonfatal myocardial infarction and a subsequent vascular death, and 1 participant had a nonfatal stroke and a subsequent vascular death (only counted once in the any cardiovascular event row); a1 participant began receiving ranibizumab prior to nonfatal stroke.

[b]One participant began receiving ranibizumab prior to nonfatal stroke.

[c]Two participants had a nonfatal stroke and a subsequent vascular death (only counted once in the any cardiovascular event row).

‡N = Number of study participants. Study participants with 2 study eyes are assigned to the non-sham group. Multiple events within a study participant are only counted once per event.

§Three of the 8 vascular deaths in the sham group, 6 of the 13 vascular deaths in the ranibizumab group, and 1 of the 8 vascular deaths in the triamcinolone group were from an unknown cause.