Intravitreal Aflibercept for Diabetic Macular Edema

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Purpose: A head-to-head comparison was performed between vascular endothelial growth factor blockade and laser for treatment of diabetic macular edema (DME).

Design: Two similarly designed, double-masked, randomized, phase 3 trials, VISTA DME and VIVID DME.

Participants: We included 872 patients (eyes) with type 1 or 2 diabetes mellitus who presented with DME with central involvement.

Methods: Eyes received either intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation.

Main Outcome Measures: The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 52. Secondary efficacy endpoints at week 52 included the proportion of eyes that gained ≥15 letters from baseline and the mean change from baseline in central retinal thickness as determined by optical coherence tomography.

Results: Mean BCVA gains from baseline to week 52 in the IAI 2q4 and 2q8 groups versus the laser group were 12.5 and 10.7 versus 0.2 letters (P < 0.0001) in VISTA, and 10.5 and 10.7 versus 1.2 letters (P < 0.0001) in VIVID. The corresponding proportions of eyes gaining ≥15 letters were 41.6% and 31.1% versus 7.8% (P < 0.0001) in VISTA, and 32.4% and 33.3% versus 9.1% (P < 0.0001) in VIVID. Similar mean reductions in central retinal thickness were 135.9 and 131.8 versus 73.3 μm (P < 0.0001) in VISTA, and 195.0 and 192.4 versus 66.2 μm (P < 0.0001) in VIVID. Overall incidences of ocular and nonocular adverse events and serious adverse events, including the Anti-Platelet Trialists’ Collaboration—defined arterial thromboembolic events and vascular deaths, were similar across treatment groups.

Conclusions: At week 52, IAI demonstrated significant superiority in functional and anatomic endpoints over laser, with similar efficacy in the 2q4 and 2q8 groups despite the extended dosing interval in the 2q8 group. In general, IAI was well-tolerated. Ophthalmology 2014;1:1–8 © 2014 by the American Academy of Ophthalmology.

The growing prevalence of diabetes mellitus worldwide is predicted to increase the number of afflicted individuals to 430 million by 2030.1 Chronic hyperglycemia secondary to diabetes mellitus leads to systemic microvascular pathology throughout the body.2 The vascular beds of the retina are typically early indicators of disease progression, and the eye serves as the initial site in which vascular damage may be diagnosed early during disease progression.3 Indeed, the most common complication of diabetes is retinopathy; microaneurysms, blood—retinal barrier dysfunction, and capillary dropout are important contributors to diabetic macular edema (DME), the leading cause of blindness in working-age adults.1,4 Focal laser photocoagulation has been the standard of care to manage DME ever since the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated reduction in severe vision loss with laser directed to the leaking microaneurysms (and areas of capillary nonperfusion).5 Although a reduction in moderate and severe vision loss was demonstrated with ETDRS laser intervention, <3% of treated patients gained 15 visual acuity letters.6 Compared with the ETDRS study, a higher percentage of eyes (15%) treated with a modified ETDRS laser protocol gained ≥15 visual acuity letters at 1 year in the Diabetes Retinopathy Clinical Research Network (DRCR.net) trial.6,7 Recently, as a result of the RISE/RISE studies, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have progressively replaced focal laser photocoagulation as the primary treatment for center involving macular edema. Anti-VEGF treatment administered monthly demonstrated significant visual acuity gains in a large percentage of patients and reduction of severe visual acuity loss when administered along with pro re nata (PRN) laser.8 Although the RISE/RISE studies, among others, resulted in a shift of the treatment paradigm for DME,
many patients in clinical practice may find a monthly treatment schedule difficult to maintain.

Afibercept is composed of key domains from human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1 and has approximately 100-fold greater binding affinity to VEGF-A than either bevacizumab or ranibizumab.8 Intravitreal afibercept injection (IAI; also known in the scientific literature as VEGF Trap-Eye or IVT-AFL) was recently demonstrated to have clinically equivalent efficacy to monthly ranibizumab in neovascular age-related macular degeneration, whether it was administered monthly or by a more convenient regimen every 2 months after 3 initial monthly doses.9 We report here the primary outcome results of 2 parallel, phase 3 DME studies in diverse North American, European, Asian, and Australian patient populations. These studies, VISTA-DME and VIVID-DME, compared, at week 52 the efficacy and safety of focal laser photocoagulation (with sham intraocular injections) with IAI either every 4 weeks or every 8 weeks, after 5 initial monthly doses. These are the first phase 3 studies directly comparing VEGF-blockade alone with laser alone in DME.

Methods

The VISTA and VIVID studies were 2 phase 3, randomized, double-masked, active-controlled, 148-week trials. The VISTA study (registered at www.clinicaltrials.gov; NCT01363440) was conducted across 54 sites in the United States and the VIVID study (registered at www.clinicaltrials.gov; NCT01331681) was conducted at 73 sites across Europe, Japan, and Australia (Appendix 1 provides a list of study investigators; available at www.aaojournal.org). Each clinical site’s respective institutional review board/ethics committee approved the study. All patients provided written informed consent. Data for this report, which presents the 52-week results, were collected between May 2011 and June 2013.

Participants and Treatments

Adult patients with type 1 or 2 diabetes mellitus who presented with central DME involvement (defined as retinal thickening involving the 1 mm central (optical coherence tomography) subfield thickness (CST)) were eligible for enrollment if best-corrected visual acuity (BCVA) was between 73 and 24 letters (20/40–20/320 Snellen equivalent) in the study eye (Appendix 2; available at www.aaojournal.org). Only 1 eye per patient was enrolled in the study. Eyes were randomized in a 1:1:1 ratio to receive either 2 mg IAI every 4 weeks (2q4), 2 mg IAI every 8 weeks after 5 initial monthly doses (from baseline to week 16) with sham injections on non-treatment visits (2q8), or macular laser photocoagulation at baseline and sham injections at every visit (laser control group). For the primary outcome at week 52, treatments were given as described from baseline to week 48 (Appendix 3; available at www.aaojournal.org); however, the studies continued with the dosing regimens as described for the IAI groups through week 148. Eyes in the laser group received IAI as needed during the third year.

Study eyes in all treatment groups were assessed for laser retreatment beginning at week 12. If any ETDRS-defined, clinically significant macular edema, for which laser has been shown to be visually beneficial, was present (defined as thickening of retina or hard exudates at ≤500 μm of center of the macula, or ≥1 zone of retinal thickening 1 disc area or larger, any part of which was within 1 disc diameter of center of the macula), study eyes in the 2q4 and 2q8 groups received sham laser and those in the laser group received active laser, but not more frequently than every 12 weeks.

Study eyes in all treatment groups could also receive additional (rescue) treatment from week 24 onward if they lost, owing to worsening DME, ≥10 letters on 2 consecutive visits or ≥15 letters at any 1 visit from the best previous measurement, and BCVA was worse than baseline. When criteria for additional treatment were met, study eyes in the 2q4 and 2q8 groups received active laser (rather than sham) from week 24 onward, whereas those in the laser group received 5 doses of 2 mg IAI every 4 weeks followed by dosing every 8 weeks.

Outcome Measures

The primary efficacy endpoint was the change from baseline in BCVA in ETDRS letters at week 52. The secondary efficacy endpoints were (a) proportion of eyes that gained ≥10 letters from baseline, (b) proportion of eyes that gained ≥15 letters from baseline, (c) proportion of eyes with a ≥2-step improvement in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score, (d) change from baseline in CST, as determined by optical coherence tomography, (e) change from baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) near activities subscale score, and (f) change from baseline in the NEI VFQ-25 distance activities subscale score. Methodologies for measuring outcomes are described in Appendix 4 (available at www.aaojournal.org).

Statistical Analyses

Efficacy was evaluated in the full analysis sets (eyes that received study treatment and had a baseline and ≥1 post-baseline BCVA assessment) from each individual study. If either of the IAI groups was superior to laser in the primary efficacy endpoint, comparisons between this IAI group and laser for the secondary efficacy endpoints were then performed in a hierarchical order from (a) to (f)—as described under Outcome Measures—to control for multiplicity. Both primary and secondary efficacy endpoints were evaluated at a 2-sided significance level of 2.5%. Missing values were imputed using the last observation carried forward (LOCF) method, and for eyes that received additional treatment, the last value before additional treatment was used for analyses, censoring values after additional treatment (LOCF). Prespecified sensitivity analyses were also performed to include values after additional treatment was given (aLOCF). Safety was assessed on the integrated safety set from VISTA and VIVID, including all randomized patients who received any study treatment. Statistical methods and sample size calculation are described in Appendix 5 (available at www.aaojournal.org).

Results

Patient Disposition, Baseline Characteristics, and Treatment Experience

The VISTA study randomized 466 patients and VIVID, 406 patients, each with 1 study eye (Appendix 6; available at www.aaojournal.org). Overall, demographics and baseline characteristics of patients were similar across all treatment groups in both studies (Table 1). However, VISTA included a greater proportion of Black or African-American patients and VIVID had a greater proportion of Asian patients. In addition, more eyes in VISTA had prior anti-VEGF therapy for DME compared with VIVID (42.9% vs 8.9%, respectively). Study eyes in the 2q4 and 2q8 groups received a mean of 11.8 and 8.4 injections in VISTA, and 12.2 and 8.7 injections in VIVID,
2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; BCVA = best-corrected visual acuity; DRSS = Diabetic Retinopathy Severity Scale; IAI = intravitreal aflibercept injection; HbA1c = hemoglobin A1c; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire —25; SD = standard deviation; VEGF = vascular endothelial growth factor.

Full analysis set.

*In VISTA included American Indian or Alaska native, Native Hawaiian or other Pacific islander, and not reported, and in VIVID included multiclinic patients.

1Level 10, none; levels 14, 15, 20, 35, and 43, mild to moderate nonproliferative diabetic retinopathy; levels 47 and 53, moderately severe/severe nonproliferative diabetic retinopathy; levels 61, 65, 71, 75, 81, and 85, mild/moderate/high-risk/advanced proliferative diabetic retinopathy.

respectively (Table 2). Eyes in the laser group received an average of 2.7 and 2.1 laser treatments in VISTA and VIVID, respectively. Additional (rescue) treatment in VISTA was given to 0.7% to 2.6% of eyes in the IAI groups compared with 31.2% of eyes in the laser group, and in VIVID to 4.4% to 8.1% of eyes in the IAI groups compared with 24.1% of eyes in the laser group (Table 2).

**Primary and Secondary Endpoints**

In both VISTA and VIVID, eyes treated with IAI 2q4 and 2q8 had significant BCVA improvements from baseline when compared with the laser group. The mean values ± standard deviation (SD) change from baseline BCVA in the 2q4 and 2q8 groups compared with the laser group was +12.5 ± 9.5 letters and +10.7 ± 8.2 letters versus +0.2 ± 12.5 letters (P < 0.0001) in VISTA, and +10.5 ± 9.5 letters and +10.7 ± 9.3 letters versus +1.2 ± 10.6 letters (P < 0.0001) in VIVID, respectively (Fig 1A). The between-group differences remained significant in favor of the IAI groups when values after additional (rescue) treatments were included in the analyses (Fig 1B). In both studies, BCVA gains with both IAI regimens were similar and significantly greater than laser in the subgroups of eyes with and without prior anti-VEGF therapy (Table 3; available at www.aaojournal.org).

In both VISTA and VIVID, significantly more eyes treated with IAI gained ≥10 and ≥15 letters from baseline at week 52. The proportion of eyes that gained ≥10 letters from baseline in the 2q4 and 2q8 groups compared with the laser group was 64.9% and 58.3% versus 19.5% (P < 0.0001) in VISTA, and 54.4% and 53.3% versus 25.8% (P < 0.0001) in VIVID, respectively (Fig 1C). The corresponding percentages for eyes that gained ≥15 letters were 41.6% and 31.1% versus 7.8% (P < 0.0001) in VISTA, and 32.4% and 33.3% versus 9.1% (P < 0.0001) in VIVID, respectively (Fig 1C). The proportion of eyes that lost ≥15 letters from baseline in the 2q4 and 2q8 groups compared with the laser group was 0.6% and 0.7% versus 9.1% in VISTA, and 0.7% and 0% versus 10.6% in VIVID, respectively. The proportion of patients who did not lose any letters from baseline values after additional (rescue) treatments were included in the analyses was 77.5% and 77.3% versus 16.2% and 16.2% in VISTA and 71.2% and 71.2% versus 17.8% and 17.8% in VIVID, respectively (Fig 1C).
**Table 2. Treatment Experience from Baseline to Week 52**

<table>
<thead>
<tr>
<th>Number of Scheduled Treatments, Mean (SD)</th>
<th>VISTA</th>
<th>VIVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser (n = 154)</td>
<td>IAI 2q4 (n = 155)</td>
<td>IAI 2q8 (n = 152)</td>
</tr>
<tr>
<td>Laser photocoagulation</td>
<td>2.7 (1.1)</td>
<td>2.1 (1.1)</td>
</tr>
<tr>
<td>Intravitreal aflibercept</td>
<td>118 (2.6)</td>
<td>8.4 (1.3)</td>
</tr>
<tr>
<td>Study eyes that received additional treatment,* n (%)</td>
<td>48 (31.2)*</td>
<td>4 (2.6)*</td>
</tr>
</tbody>
</table>

*“-” = not applicable; 2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 48 (5 doses) followed by dosing every 8 weeks through week 48; IAI = intravitreal aflibercept injection; SD = standard deviation.

Safety analysis set.

*Additional treatment was 2 mg IAI every 4 weeks for 5 initial doses followed by dosing every 8 weeks in the laser group, and active laser for the IAI 2q4 and 2q8 groups. Eyes in the laser group that qualified for additional treatment (48 eyes in VISTA and 32 eyes in VIVID) received a mean ± SD of 4.4 ± 1.6 and 4.2 ± 1.8 injections of IAI, respectively. Eyes in the 2q4 and 2q8 groups (4 and 1, respectively, in VISTA; 6 and 11 in VIVID) that qualified for additional treatment received a mean ± SD of 1.0 ± 0 and 1.0 ± NE (not evaluable) laser in VISTA, and 1.7 ± 0.5 and 1.5 ± 0.5 lasers in VIVID, respectively.

in the 2q4 and 2q8 groups compared with the laser group was 94.2% and 92.7% versus 57.1% in VISTA, and 94.1% and 91.9% versus 62.9% in VIVID, respectively.

Significantly greater proportions of eyes treated with IAI 2q4 and 2q8 compared with those treated with laser had a ≥2-step improvement in DRSS score in both VISTA (33.8% and 29.1% versus 14.3%, respectively; *P* < 0.01) and VIVID (33.3% and 27.7% versus 7.5%, respectively; *P* < 0.001; Fig 2A). The mean value ± SD improvements from baseline in CST were robust throughout the study and were significantly greater at week 52 in the 2q4 and 2q8 groups compared with the laser group in both VISTA (−185.9 ± 150.7 μm and −183.1 ± 153.5 μm vs −73.3 ± 176.7 μm, respectively; *P* < 0.0001) and VIVID (−195.0 ± 146.6 μm and −192.4 ± 149.9 μm vs −66.2 ± 139.0 μm, respectively; *P* < 0.0001; Fig 2B). The mean ± SD change from baseline in NEI VFQ-25 score was significantly different only for the near activities subscale in favor of IAI 2q4 compared with laser in VISTA (9.0 ± 0.6 vs 5.4 ± 20.4, respectively; *P* = 0.0168; Fig 3; available at www.aaojournal.org). The NEI VFQ-25 subscale scores were similar across all treatment groups in VIVID (Fig 3; available at www.aaojournal.org).

**Adverse Events**

The overall incidences of ocular and nonocular adverse events were similar across treatment groups (Appendix 7; available at www.aaojournal.org). There were no clinically relevant differences between the treatment groups in terms of frequency or pattern of ocular serious adverse events (Table 4). There were no reports of endophthalmitis, or events suggestive of endophthalmitis (such as hypopyon). The incidence of intraocular inflammation, based on the total number of intravitreal injections in the IAI 2q4, IAI 2q8, and laser groups was 0.2% (4/1832 injections), 0.1% (1/1284 injections), and 0.5% (1/212 injections) in VISTA, and 0.2% (4/1656 injections), 0.4% (5/1168 injections), and 0.7% (1/135 injections) in VIVID, respectively. However, both laser patients developed intraocular inflammation prior to receiving IAI.

The incidence of nonocular serious adverse events was slightly higher for some events in the combined IAI group (e.g., congestive cardiac failure and anemia), and for others in the laser group (e.g., acute myocardial infarction and osteoarthritis), with no apparent general trend (Appendix 7; available at www.aaojournal.org). The overall incidences of nonocular serious adverse events and arterial thromboembolic events defined by the Anti-Platelet Trialists’ Collaboration criteria were similar across treatment groups (Appendix 7; available at www.aaojournal.org; Table 4). The number of vascular deaths in the 2q4, 2q8, and laser groups was 2, 2, and 2, respectively (Appendix 7; available at www.aaojournal.org). The total number of deaths in these groups was 2, 4, and 2, respectively, with the 2 additional nonvascular deaths in the 2q8 group attributed to B-cell lymphoma and lung neoplasm (Appendix 7; available at www.aaojournal.org). The incidences and patterns of deaths were not clinically different among treatment groups.

**Discussion**

The VIVID and VISTA studies provide the first head-to-head comparisons of anti-VEGF blockade alone versus laser therapy alone. The results demonstrate that IAI given either every 4 or every 8 weeks (after 5 initial monthly doses) is superior to laser and results in both significant visual acuity gains and prevention of severe visual acuity loss. The primary efficacy endpoint (change from baseline in BCVA at 52 weeks) was superior in both 2q4 and 2q8 groups compared with the laser group in both studies. The percentage of eyes in the laser group that lost ≥15 letters of vision was 9.1% in VISTA and 10.6% in VIVID, replicating the 10% loss in the laser group reported by the ETDRS study.5 In the DRCR.net trial, 8.0% of eyes treated with a modified ETDRS laser protocol lost ≥15 letters at 1 year. In marked contrast, <1% of eyes in the IAI groups (both 2q4 and 2q8) had severe visual acuity loss. An additional benefit noted in both the IAI 2q4 and 2q8 groups include significant improvement in DRSS score, implying regression of the underlying diabetic retinopathy beyond the macular area.

The VISTA/VIVID trial design differs in several respects from previous anti-VEGF DME trials.7,11,12 First, the trial included multiethnic populations; approximately 20% of patients in VIVID were Asian compared with approximately 43% of study eyes in VISTA had been previously treated with anti-VEGF agents (with a ≥3-month washout period) demonstrating efficacy in eyes that were not totally naïve to anti-VEGF therapy. The VISTA/VIVID trials also differed from the RISE/RIDE trials in that the active anti-VEGF agent was compared with an active control group (laser),
Figure 1. Visual outcomes from baseline to week 52. A, Mean ± standard deviation (SD) change in best-corrected visual acuity (BCVA) from baseline through week 52 with censoring of values after additional treatment was given (LOCF). B, Mean ± SD change in BCVA from baseline through week 52 with inclusion of values after additional treatment was given (aLOCF). C, Proportion of eyes that gained ≥10 and ≥15 letters from baseline to week 52 (LOCF). Full analysis set. In VISTA, n = 154 for laser, n = 154 for intravitreal aflibercept injection (IAI) 2q4, and n = 151 for IAI 2q8. In VIVID, n = 132 for laser, n = 136 for IAI 2q4, and n = 135 for IAI 2q8. ***P < 0.0001 versus laser from the analysis of covariance (ANCOVA) model for A and B, and Cochran-Mantel-Haenszel (CMH) test for C. 2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; aLOCF = last observation carried forward, including values after additional treatment was given; LOCF = last observation carried forward, censoring values after additional treatment was given; CMH = Cochran-Mantel-Haenszel; SD = standard deviation.
whereas the RISE/RIDE trials compared ranibizumab with sham injections. In the RISE/RIDE studies, PRN laser was available to all groups after 3 months, based on predefined anatomic criteria. In contrast, the IAI groups in VIVID/VISTA could only receive laser as a rescue treatment after 24 weeks, based on significant visual acuity loss. Few eyes (<10%) in the IAI 2q4 and 2q8 groups required laser rescue and data from the time rescue laser was given was censored for the primary analysis (LOCF), thus eliminating any confounding influence from laser photocoagulation (Fig 1A). When data after additional treatment was included in the analysis (aLOCF), similar improvements were observed in the mean BCVA for these groups (Fig 1B).

Although the variability in CST in the IAI 2q8 group may suggest that anatomic suppression was not continuous with every 8-week dosing, the visual acuity results indicate that a large majority of patients with DME may be effectively treated with every 8-week dosing, given that >90% of patients in the 2q8 group did not lose any vision. Importantly, similar to the VIEW studies in patients with neovascular age-related macular degeneration, there was no evidence that these optical coherence tomography fluctuations adversely translated into any corresponding limitation in visual benefit in DME patients.

Concerns about the potential systemic effects of intravitreal anti-VEGF agents are particularly relevant in the diabetic population, because a large population of diabetic patients have silent ischemia in the coronary circulation. In the RISE/RIDE trials, the 0.5-mg dose of ranibizumab had relatively higher rates of stroke and death compared with the 0.3-mg dose. Ranibizumab has been approved in the United States at the lower dose of 0.3 mg, and in Europe at the dose of 0.5 mg. It is noteworthy that no increased rate of death, stroke, or myocardial infarction was seen in VISTA or VIVID in the IAI 2q4 group at the 52-week primary endpoint. Although differences in rates of infrequent events may not be easily detected in studies including relatively small patient populations, ongoing surveillance will continue to assess if there are any potential systemic

Figure 2. Additional key secondary endpoints. A, Proportion of eyes with a ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score from baseline to week 52. Full analysis set; last observation carried forward, censoring values after additional treatment was given (LOCF). In VISTA, n = 154 for laser, n = 154 for intravitreal aflibercept injection (IAI) 2q4, and n = 151 for IAI 2q8. In VIVID, n = 80 for laser, n = 81 for IAI 2q4, and n = 83 for IAI 2q8. B, Mean change from baseline in central (optical coherence tomography) subfield thickness (CST) at each study visit through week 52. Full analysis set; LOCF. In VISTA, n = 154 for laser, n = 154 for IAI 2q4, and n = 151 for IAI 2q8. In VIVID, n = 132 for laser, n = 136 for IAI 2q4, and n = 135 for IAI 2q8. *P < 0.01, **P < 0.001, and ***P < 0.0001 versus laser. 2q4 = 2 mg IAI every 4 weeks from baseline to week 48; 2q8 = 2 mg IAI every 4 weeks from baseline to week 16 (5 doses) followed by dosing every 8 weeks through week 48; LOCF = last observation carried forward, censoring values after additional treatment was given.
In summary, the 1-year results of the VISTA/VIVID studies demonstrate that IAI delivered every 4 or every 8 weeks (after 5 initial monthly doses) significantly improved visual outcomes and significantly decreased severe vision loss, while simultaneously improving the diabetic retinopathy severity score, compared with focal laser photocoagulation. Data from these ongoing studies will provide additional information regarding the similar efficacy observed with the 2q4 and 2q8 regimens of IAI. Thus, intravitreal aflibercept dosed every 8 weeks (after 5 initial monthly doses) could provide a therapeutic option that may reduce the total number of injections and necessary office visits, substantially reducing burden on patients, physicians, and the health care system.

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Abbreviations and Acronyms:
• aLOCF = last observation carried forward, including values after additional treatment was given; BCVA = best-corrected visual acuity; CST = central (optical coherence tomography) subfield thickness; DME = diabetic macular edema; DRCR.net = Diabetes Retinopathy Clinical Research Network; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; IAI = intravitreal aflibercept injection; LOCF = last observation carried forward, censoring values after additional treatment was given; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; PRN = pro re nata; VEGF = vascular endothelial growth factor.

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