

Intravitreal Aflibercept for Diabetic Macular Edema

100-Week Results From the VISTA and VIVID Studies

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Purpose: To compare efficacy and safety of 2 dosing regimens of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME).

Design: Two similarly designed, randomized, phase 3 trials, VISTA^{DME} and VIVID^{DME}.

Participants: Patients (eyes; n = 872) with type 1 or 2 diabetes mellitus who had DME with central involvement.

Methods: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control.

Main Outcome Measures: The primary end point was mean change from baseline in best-corrected visual acuity (BCVA) at week 52. This report presents the 100-week results including mean change from baseline in BCVA, proportion of eyes that gained ≥ 15 letters, and proportion of eyes with a ≥ 2 -step improvement in the Diabetic Retinopathy Severity Scale (DRSS) score.

Results: Mean BCVA gain from baseline to week 100 with IAI 2q4, IAI 2q8, and laser control was 11.5, 11.1, and 0.9 letters ($P < 0.0001$) in VISTA and 11.4, 9.4, and 0.7 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained ≥ 15 letters from baseline at week 100 was 38.3%, 33.1%, and 13.0% ($P < 0.0001$) in VISTA and 38.2%, 31.1%, and 12.1% ($P \leq 0.0001$) in VIVID. The proportion of eyes that lost ≥ 15 letters at week 100 was 3.2%, 0.7%, and 9.7% ($P \leq 0.0220$) in VISTA and 2.2%, 1.5%, and 12.9% ($P \leq 0.0008$) in VIVID. Significantly more eyes in the IAI 2q4 and 2q8 groups versus those in the laser control group had a ≥ 2 step improvement in the DRSS score in both VISTA (37.0% and 37.1% vs. 15.6%; $P < 0.0001$) and VIVID (29.3% and 32.6% vs. 8.2%; $P \leq 0.0004$). In an integrated safety analysis, the most frequent serious ocular adverse event was cataract (2.4%, 1.0%, and 0.3% for 2q4, 2q8, and control).

Conclusions: In both VISTA and VIVID, the 52-week visual and anatomic superiority of IAI over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups. Safety in these studies was consistent with the known safety profile of IAI. *Ophthalmology* 2015;122:2044-2052 © 2015 by the American Academy of Ophthalmology.



Supplemental material is available at www.aaojournal.org.

Diabetic retinopathy is the most common microvascular complication of diabetes mellitus and the leading cause of blindness in working-age adults in the United States, Europe, and increasingly worldwide.¹⁻⁴ Diabetic macular edema (DME) is a major cause of the vision loss associated with diabetic retinopathy¹ and is characterized by exudation and accumulation of extracellular fluid in the macula⁵ secondary to an increase in vascular permeability.⁶ In 2010, of an estimated 92.6 million adults with diabetic retinopathy worldwide, 20.6 million were estimated to have DME.⁷ The global prevalence of DME is likely to increase along with the increasing prevalence of diabetes.²

Beginning with the Early Treatment Diabetic Retinopathy Study (ETDRS) in the 1980s, laser photocoagulation has been the standard of care for the treatment of DME.⁸ This treatment reduced the risk of visual loss in patients with clinically significant DME and mild to moderate diabetic retinopathy, but had limited effectiveness in improving vision.⁸ Corticosteroids (i.e., dexamethasone, triamcinolone acetonide, and fluocinolone acetonide) also have been used to treat DME. Although corticosteroids are effective, their use is associated with high rates of increased intraocular pressure and cataract.⁹ Recent evidence has highlighted the role of vascular endothelial growth factor (VEGF) in the

pathophysiology of diabetic retinopathy and DME.^{10,11} Several clinical trials have demonstrated a favorable efficacy and safety profile for anti-VEGF therapies in patients with DME, including ranibizumab, a humanized monoclonal anti-VEGF antibody fragment,^{12–14} bevacizumab, a full-length humanized monoclonal anti-VEGF antibody,^{15,16} and aflibercept.¹⁷ Therefore, anti-VEGF treatment has been recommended as the first-line therapy for DME.^{13,18}

Aflibercept is a 115-kDa recombinant fusion protein comprising the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the constant region (Fc) of human immunoglobulin G1.¹⁹ Aflibercept has been shown to have a higher binding affinity to VEGF-A compared with ranibizumab and bevacizumab in preclinical studies.²⁰ Unlike ranibizumab and bevacizumab, aflibercept also binds to VEGF-B and placental growth factor,²⁰ which may contribute to vascular permeability and retinal neovascularization.²¹ Intravitreal aflibercept injection (IAI), also known in the scientific literature as “VEGF Trap Eye” or “IVT-AFL,” has been approved in the United States, European Union, Australia, and Japan to treat DME. The efficacy and safety of IAI in DME were first shown in the phase 2 DA Vinci study.^{22,23} The subsequent phase 3 studies, VISTA^{DME} and VIVID^{DME},¹⁷ demonstrated that after 52 weeks of treatment, IAI provided significantly greater improvements in visual and anatomic outcomes when compared with laser photocoagulation. Moreover, the proportion of patients with improvements on the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at week 52 was also significantly greater with IAI than with laser control, suggesting beneficial effects on the underlying diabetic retinopathy. Of note, ocular and systemic safety outcomes over the first 52 weeks of treatment were similar across all treatment groups.¹⁷ We report the 100-week results of these studies.

Methods

Study Design

VISTA and VIVID were 2 similarly designed, double-masked, randomized, active-controlled, 148-week, phase 3 trials. VISTA (registered at www.clinicaltrials.gov; NCT01363440) was

conducted across 54 sites in the United States, and VIVID (registered at www.clinicaltrials.gov; NCT01331681) was conducted in 73 sites across Europe, Japan, and Australia. Each clinical site’s respective institutional review board/ethics committee approved the study. All patients provided written informed consent. Both VISTA and VIVID were conducted in compliance with the International Conference on Harmonization guidelines and the Health Insurance Portability and Accountability Act of 1996.^{24,25} Data for this report, which presents the 100-week results, were collected between May 2011 and May 2014.

Patient eligibility for the VISTA and VIVID studies has been described.¹⁷ Briefly, adult patients with type 1 or 2 diabetes mellitus who presented with central-involved DME (defined as retinal thickening involving the 1-mm central [optical coherence tomography [OCT] 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. Only 1 eye per patient was enrolled in the study. Eyes were randomized in a 1:1:1 ratio to receive IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation at baseline and at visits in which patients met any of the laser re-treatment criteria (laser control group). Eyes were treated through week 96.

Study eyes in all treatment groups were assessed for laser re-treatment beginning at week 12. If any ETDRS-defined, clinically significant macular edema was present (defined as thickening of the retina or hard exudates at ≤ 500 μ m of center of the macula, or at least 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 eyes 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 DME worsened causing a ≥ 10 -letter loss at 2 consecutive visits or ≥ 15 -letter loss at 1 visit from the best previous measurement, with BCVA not better than baseline. When these criteria were met, study eyes in the 2q4 and 2q8 groups received active laser (rather than sham laser) from week 24 onward, and eyes in the laser control group received 5 doses of 2 mg IAI every 4 weeks followed by dosing every 8 weeks (rather than sham injections). Patients could receive both laser and IAI, when applicable, at the same visit.

Outcome Measures

The primary efficacy end point, change from baseline BCVA in ETDRS letters at week 52, has been reported.¹⁷ We report the

Table 1. Treatment Experience from Baseline to Week 100

	VISTA			VIVID		
	Laser Control (n = 154)	IAI 2q4 (n = 155)	IAI 2q8 (n = 152)	Laser Control (n = 133)	IAI 2q4 (n = 136)	IAI 2q8 (n = 135)
No. of scheduled treatments, mean (SD)						
Laser photocoagulation	3.5 (2.0)	N/A	N/A	2.4 (1.6)	N/A	N/A
Intravitreal aflibercept	N/A	21.3 (5.8)	13.5 (2.9)	N/A	22.6 (5.8)	13.6 (2.9)
Study eyes that received rescue treatment,* n (%)	63 (40.9)*	5 (3.2)*	13 (8.6)*	46 (34.6)*	10 (7.4)*	15 (11.1)*

Safety analysis set.

2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 5 initial monthly doses; IAI = intravitreal aflibercept injection; N/A = not applicable; SD = standard deviation.

*Rescue treatment was 2 mg IAI every 4 weeks for 5 initial doses followed by dosing every 8 weeks in the laser control group and active laser for the IAI 2q4 and 2q8 groups. Overall, 63 laser-treated eyes in VISTA and 46 laser-treated eyes in VIVID received a mean $\pm$ SD of 8.9 ± 2.7 and 8.8 ± 2.9 injections of IAI as rescue treatment from week 24 to week 100, respectively. In the 2q4 and 2q8 groups, 5 and 13 eyes received a mean $\pm$ SD of 1.6 ± 0.9 and 1.2 ± 0.6 lasers in VISTA, whereas 10 and 15 eyes in VIVID received a mean $\pm$ SD of 1.9 ± 1.1 and 1.7 ± 0.8 lasers from week 24 to week 100, respectively.

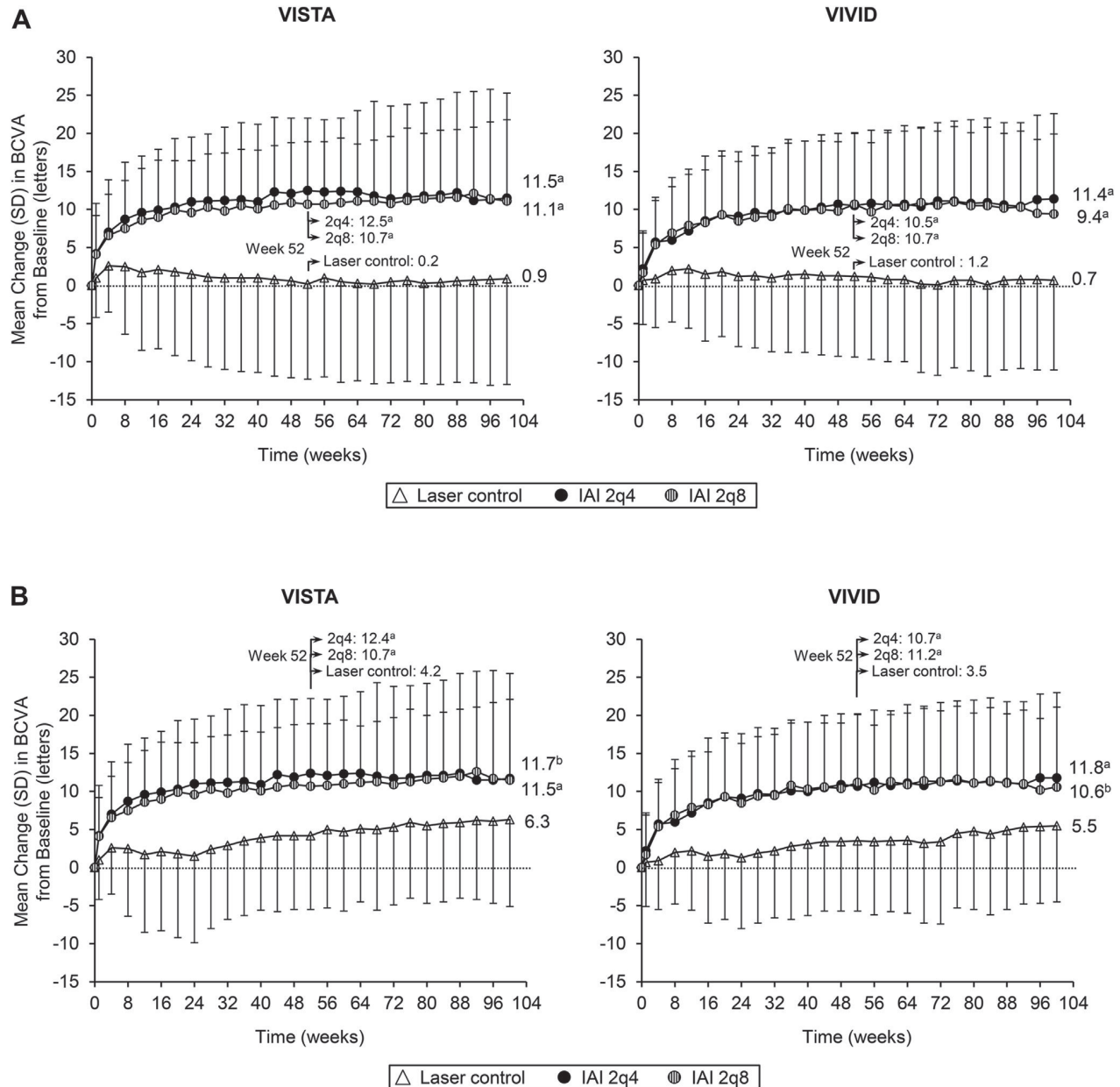


Figure 1. Best-corrected visual acuity (BCVA) from baseline to week 100. **A**, Mean $\pm$ standard deviation (SD) change in BCVA from baseline to week 100 (last observation carried forward, censoring measurements after rescue treatment was given [LOCF]). **B**, Mean $\pm$ SD change in BCVA from baseline to week 100 (last observation carried forward, including measurements after rescue treatment was given [aLOCF]). Full analysis set. In VISTA, $n = 154$ for laser control, $n = 154$ for 2 mg intravitreal aflibercept injection (IAI) every 4 weeks (2q4), and $n = 151$ for IAI 2 mg every 8 weeks after 5 initial monthly doses (2q8). In VIVID, $n = 132$ for laser control, $n = 136$ for IAI 2q4, and $n = 135$ for IAI 2q8. ^a $P < 0.0001$ and ^b $P = 0.0002$ versus laser control from the analysis of covariance.

100-week results of the VISTA and VIVID studies. Prespecified efficacy end points at week 100 were exploratory and included the mean change from baseline in BCVA; proportion of eyes that gained ≥ 0 , ≥ 5 , ≥ 10 , and ≥ 15 letters or lost ≥ 5 , ≥ 10 , and ≥ 15 letters from baseline; proportion of eyes with a ≥ 2 -step improvement from baseline in the DRSS score²⁶; change from baseline in CST as determined by spectral-domain OCT; and change from baseline in the National Eye Institute Visual Function

Questionnaire-25 (NEI VFQ-25) near and distance activities sub-scale scores.

The BCVA using the ETDRS protocol⁸ and CST using spectral domain OCT were assessed every 4 weeks. Fluorescein angiography, fundus photography, and assessment of vision-related quality of life using NEI VFQ-25 were performed at baseline and weeks 24, 52, 72, and 100. Masked graders at independent central reading centers evaluated OCT images for CST

Table 2. Eyes with Vision Gains and Losses from Baseline at Week 100

	VISTA				VIVID			
	Laser Control (n = 154)	IAI 2q4 (n = 154)	IAI 2q8 (n = 151)	P Value	Laser Control (n = 132)	IAI 2q4 (n = 136)	IAI 2q8 (n = 135)	P Value
Vision Gain, n (%)								
≥15 letters	20 (13.0)	59 (38.3)	50 (33.1)	<0.0001*	16 (12.1)	52 (38.2)	42 (31.1)	≤0.0001† 0.0001‡
≥10 letters	43 (27.9)	98 (63.6)	90 (59.6)	<0.0001*	33 (25.0)	79 (58.1)	67 (49.6)	<0.0001*
≥5 letters	62 (40.3)	125 (81.2)	118 (78.1)	<0.0001*	51 (38.6)	108 (79.4)	97 (71.9)	<0.0001*
≥0 letters	84 (54.5)	139 (90.3)	135 (89.4)	<0.0001*	74 (56.1)	126 (92.6)	112 (83.0)	<0.0001*
Vision Loss, n (%)								
≥5 letters	49 (31.8)	9 (5.8)	7 (4.6)	<0.0001*	40 (30.3)	5 (3.7)	14 (10.4)	<0.0001*
≥10 letters	30 (19.5)	6 (3.9)	2 (1.3)	<0.0001*	25 (18.9)	4 (2.9)	5 (3.7)	<0.0001*
≥15 letters	15 (9.7)	5 (3.2)	1 (0.7)	0.0220† 0.0004‡	17 (12.9)	3 (2.2)	2 (1.5)	0.0008† 0.0002‡

Full analysis set.

2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 5 initial monthly doses; IAI = intravitreal aflibercept injection; LOCF = last observation carried forward, censoring measurements after rescue treatment was given.

*For both IAI 2q4 and 2q8 compared with laser control.

†For IAI 2q4 compared with laser control.

‡For IAI 2q8 compared with laser control.

(Duke Reading Center, Durham, NC for VISTA, and Vienna Reading Center, Vienna, Austria for VIVID) and fundus images including assessment of the DRSS score (Digital Angiography Reading Center, Great Neck, NY for VISTA, and Vienna Reading Center, Vienna, Austria for VIVID).

Statistical Analyses

Efficacy end points were evaluated at a 2-sided significance level of 2.5% in the full analysis sets from each individual study. The full analysis sets included eyes that received study treatment and had a baseline and at least 1 post-baseline BCVA assessment. Continuous variables were analyzed with an analysis of covariance with the baseline value as covariate and treatment group and geographic region (VIVID only) or medical history of myocardial infarction or cerebrovascular accident (VISTA only) as fixed factors. Proportions were analyzed using a Cochran–Mantel–Haenszel test stratified by geographic region (VIVID) and history of myocardial infarction or cerebrovascular accident (VISTA). Missing values were imputed using the last observation carried forward method, and for eyes that received rescue treatment, the last value before rescue treatment was used for analyses, censoring measurements after rescue treatment was given (LOCF). Prespecified sensitivity analyses were also performed to include values after rescue treatment was given (aLOCF). All outcome measures at week 100 were analyzed in an exploratory manner, and *P* values reported are considered nominal. Safety was assessed on the integrated safety set from VISTA and VIVID, including all randomized patients who received any study treatment.

Results

Patient Disposition, Baseline Characteristics, and Treatment Experience

VISTA randomized and treated 461 patients, and VIVID randomized and treated 404 patients, each with 1 study eye (Appendix 1, available at www.aaojournal.org). Overall, the demographics and baseline characteristics of patients were similar across

all treatment groups in both studies.¹⁷ As reported previously, VISTA included a higher proportion of Black or African-American patients and VIVID had a higher proportion of Asian patients. In addition, significantly more eyes in VISTA had prior anti-VEGF therapy for DME compared with VIVID (42.9% vs. 8.9%, respectively). Overall, 82.6% of eyes in VISTA and 81.3% of eyes in VIVID completed the study through week 100 (Appendix 1, available at www.aaojournal.org). From baseline to week 100, study eyes in the IAI 2q4 and 2q8 groups received a mean of 21.3 and 13.5 injections in VISTA and 22.6 and 13.6 injections in VIVID, respectively (Table 1). Eyes in the laser control group received an average of 3.5 and 2.4 laser treatments in VISTA and VIVID, respectively. Rescue treatment in VISTA was given to 3.2% and 8.6% of eyes in the 2q4 and 2q8 groups compared with 40.9% of eyes in the laser control group, and in VIVID was given to 7.4% and 11.1% of eyes in the 2q4 and 2q8 groups compared with 34.6% of eyes in the laser control group, respectively (Table 1).

Efficacy Outcomes

In both VISTA and VIVID, eyes with DME treated with IAI 2q4 and 2q8 demonstrated sustained visual acuity gains through week 100. The mean ± standard deviation (SD) change from baseline BCVA in the 2q4 and 2q8 groups at week 100 was +11.5±13.8 and +11.1±10.7 letters versus +0.9±13.9 letters in the laser control group (*P* < 0.0001 for both), respectively in VISTA, and +11.4±11.2 and +9.4±10.5 letters versus +0.7±11.8 letters (*P* < 0.0001 for both), respectively in VIVID (Fig 1A). Although this analysis (LOCF) censored data from the time rescue treatment was given (Fig 1A), the between-group differences remained in favor of the IAI groups when values after rescue treatment were included in the analyses (aLOCF) (Fig 1B).

In both VISTA and VIVID, significantly more eyes treated with IAI gained ≥0, ≥5, ≥10, and ≥15 letters, whereas significantly more eyes treated with laser control lost ≥5, ≥10, and ≥15 letters from baseline at week 100 (Table 2). The proportion of eyes that gained ≥15 letters from baseline in the 2q4 and 2q8 groups compared with the laser control group was 38.3% and 33.1%

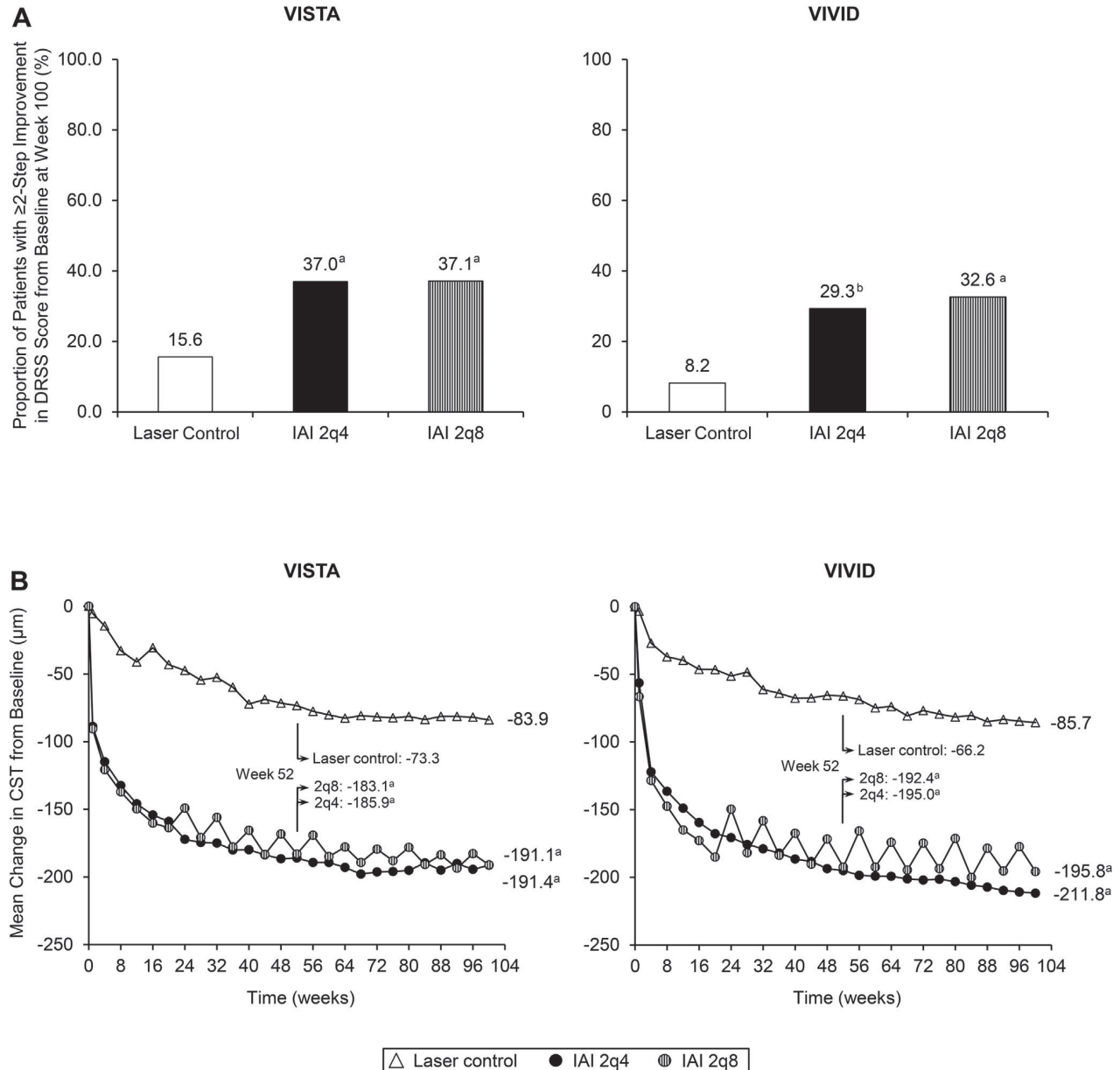


Figure 2. Changes in Diabetic Retinopathy Severity Scale (DRSS) score and central subfield thickness (CST) outcome measures. **A**, Proportion of eyes with a ≥ 2 -step improvement in DRSS score from baseline at week 100 (last observation carried forward, censoring measurements after rescue treatment was given [LOCF]). In VISTA, analyses were performed using the full analysis sets. In VIVID, analyses included only evaluable patients defined as those with a gradable baseline DRSS and a post-baseline DRSS score. In VISTA, $n = 154$ for laser control, $n = 154$ for intravitreal aflibercept injection (IAI) 2q4, and $n = 151$ for IAI 2q8. In VIVID, $n = 85$ for laser control, $n = 82$ for IAI 2q4, and $n = 86$ for IAI 2q8. **B**, Mean change from baseline in CST at each study visit through week 100. Full analysis set; LOCF. In VISTA, $n = 154$ for laser control, $n = 154$ for IAI 2q4, and $n = 151$ for IAI 2q8. In VIVID, $n = 132$ for laser control, $n = 136$ for IAI 2q4, and $n = 135$ for IAI 2q8. ^a $P < 0.0001$ and ^b $P = 0.0004$. 2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 5 initial monthly doses.

versus 13.0% ($P < 0.0001$ for both), respectively, in VISTA, and 38.2% and 31.1% versus 12.1% ($P < 0.0001$ for IAI 2q4 and $P = 0.0001$ for IAI 2q8), respectively, in VIVID (Table 2). The corresponding percentages for eyes that lost ≥ 15 letters were 3.2% and 0.7% versus 9.7% ($P = 0.0220$ for IAI 2q4 and $P = 0.0004$ for IAI 2q8), respectively, in VISTA, and 2.2% and 1.5% versus 12.9% ($P = 0.0008$ for IAI 2q4 and $P = 0.0002$ for IAI 2q8), respectively, in VIVID (Table 2).

Significantly higher proportions of eyes treated with IAI 2q4 and 2q8 compared with eyes treated with laser control had at least a 2-step improvement in the DRSS score in both VISTA (37.0% and 37.1% vs. 15.6%, respectively; $P < 0.0001$ for both) and VIVID (29.3% and 32.6% vs. 8.2%, respectively; $P = 0.0004$ for IAI 2q4 and $P < 0.0001$ for IAI 2q8) (Fig 2A). The mean $\pm$ SD improvements from baseline CST in the IAI 2q4 and 2q8 groups were robust throughout the study and significantly greater than

Table 3. Ocular Serious Adverse Events from Baseline to Week 100

	Control (n = 287)	IAI 2q4 (n = 291)	IAI 2q8 (n = 287)	All IAI (n = 578)
Any ocular SAEs in study eye, n (%)	17 (5.9)	15 (5.2)	11 (3.8)	26 (4.5)
Cataract	1 (0.3)	7 (2.4)	3 (1.0)	10 (1.7)
Cataract, subcapsular	0	0	1 (0.3)	1 (0.2)
Corneal epithelium defect	1 (0.3)	0	0	0
Diabetic retinopathy	4 (1.4)	0	0	0
Hyphema	0	1 (0.3)	0	1 (0.2)
Lens dislocation	0	1 (0.3)	0	1 (0.2)
Macular degeneration	1 (0.3)	0	0	0
Punctate keratitis	0	1 (0.3)	0	1 (0.2)
Retinal artery occlusion	0	1 (0.3)	1 (0.3)	2 (0.3)
Retinal detachment	0	1 (0.3)	1 (0.3)	2 (0.3)
Retinal exudates	1 (0.3)	0	0	0
Retinal hemorrhage	1 (0.3)	0	0	0
Retinal ischemia	0	1 (0.3)	0	1 (0.2)
Retinal neovascularization	3 (1.0)	0	0	0
Retinal vascular disorder	1 (0.3)	0	0	0
Visual acuity reduced	0	1 (0.3)	1 (0.3)	2 (0.3)
Vitreous hemorrhage	5 (1.7)	3 (1.0)	2 (0.7)	5 (0.9)
Injection site injury	0	1 (0.3)	0	1 (0.2)
Intraocular pressure increased	0	0	1 (0.3)	1 (0.2)
Visual acuity test results abnormal	0	0	1 (0.3)	1 (0.2)
Visual field defect	0	0	1 (0.3)	1 (0.2)
Cataract operation	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.3)

Integrated safety analysis set.

2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 5 initial monthly doses; IAI = intravitreal aflibercept injection; SAE = serious adverse event.

those seen in the laser control group at week 100 in both VISTA ($-191.4 \pm 180.0 \mu\text{m}$ and $-191.1 \pm 160.7 \mu\text{m}$ vs. $-83.9 \pm 179.3 \mu\text{m}$, respectively; $P < 0.0001$ for both) and VIVID ($-211.8 \pm 150.9 \mu\text{m}$ and $-195.8 \pm 141.7 \mu\text{m}$ vs. $-85.7 \pm 145.8 \mu\text{m}$, respectively; $P < 0.0001$ for both) (Fig 2B).

The mean $\pm$ SD change from baseline in NEI VFQ-25 score was significantly greater for IAI 2q8 versus laser control in the near activities subscale (12.8 ± 21.4 vs. 8.1 ± 22.1 , respectively; $P = 0.0218$) and for IAI 2q4 versus laser control in the distance activities subscale (10.9 ± 22.1 vs. 6.1 ± 20.4 , respectively; $P = 0.0072$) in VISTA (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

Overall incidences of ocular and nonocular adverse events (AEs) were similar across treatment groups (Appendix 2, available at www.aaojournal.org). There were no clinically relevant differences between the treatment groups in terms of frequency

or pattern of ocular serious AEs (Table 3). There were no reports of endophthalmitis or events suggestive of endophthalmitis (e.g., hypopyon) in the study eyes. The incidence of intraocular inflammation based on the total number of intravitreal injections in the IAI 2q4, IAI 2q8, and control groups was 0.2% (7/3308 injections), 0.2% (3/2053 injections), and 0.4% (2/559 injections), respectively, in VISTA, and 0.2% (5/3077 injections), 0.3% (5/1838 injections), and 0.3% (1/403 injections), respectively, in VIVID. However, the 3 eyes in the control group that developed intraocular inflammation did so before receiving any intravitreal aflibercept. The incidence of nonocular serious AEs was slightly higher for some events in the combined IAI group (e.g., anemia and cerebrovascular accident) and for others in the control group (e.g., acute myocardial infarction and acute cardiac failure), with no apparent general trend (Appendix 2, available at www.aaojournal.org). The incidences of arterial thromboembolic events defined by the Anti-Platelet Trialists' Collaboration criteria were low and comparable across treatment groups (Table 4). The incidence of death in the IAI 2q4, IAI 2q8,

Table 4. Anti-Platelet Trialists' Collaboration—Defined Arterial Thromboembolic Events from Baseline to Week 100

	Control (n = 287)	IAI 2q4 (n = 291)	IAI 2q8 (n = 287)	All IAI (n = 578)
Any APTC-ATEs,* n (%)	12 (4.2)	21 (7.2)	16 (5.6)	37 (6.4)
Nonfatal myocardial infarction	7 (2.4)	9 (3.1)	5 (1.7)	14 (2.4)
Nonfatal stroke	3 (1.0)	6 (2.1)	6 (2.1)	12 (2.1)
Vascular death	3 (1.0)	7 (2.4)	6 (2.1)	13 (2.2)

Integrated safety analysis set.

2q4 = 2 mg every 4 weeks; 2q8 = 2 mg every 8 weeks after 5 initial monthly doses; APTC-ATEs = Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events; IAI = intravitreal aflibercept injection.

*Adjudicated by a masked committee.

and control groups was 5.2%, 2.6%, and 1.9%, respectively, in VISTA, and 2.9%, 4.4%, and 0.8%, respectively, in VIVID. In VISTA, the IAI 2q4 group had the highest incidence of death, but this was not replicated in VIVID, and no dose response was apparent. A listing of causes of death is presented in [Appendix 2](#) (available at www.aaojournal.org).

Discussion

The week 100 results of the VISTA and VIVID trials show that the improvements in visual and anatomic outcomes achieved with IAI 2q4 and IAI 2q8, as well as the superiority of IAI over laser control at week 52, were all maintained over 100 weeks of treatment. Mean BCVA changes from baseline to week 100 were significantly greater in eyes treated with IAI compared with laser control, and significantly greater proportions of IAI-treated eyes gained ≥ 15 letters at week 100. In both studies, a significantly greater proportion of eyes treated with IAI experienced an improvement of ≥ 2 steps in the DRSS score compared with eyes treated with laser control, suggesting that IAI also may promote regression of the underlying diabetic retinopathy in addition to the treatment of DME. Improvements from baseline in CST also were greater in eyes treated with IAI compared with laser control, and there was no evidence that the observed fluctuations in CST ([Fig 2B](#), post-week 20) were associated with any limitation in visual benefit over the 100 weeks of follow-up.

Several studies have shown that intravitreal injections of ranibizumab and bevacizumab are also superior to laser in DME.^{12,18,27,28} A randomized, comparative study of anti-VEGF agents recently demonstrated that IAI provided significantly greater efficacy, despite 1 fewer injection and fewer laser rescue treatments, than ranibizumab and bevacizumab.²⁹ The improvements with IAI relative to ranibizumab and bevacizumab were primarily driven by patients with baseline visual acuity $<20/40$. In these patients, the IAI group had a statistically significant 7-letter improvement over bevacizumab and a 5-letter improvement over ranibizumab (intravitreal aflibercept +19 letters; bevacizumab +12; ranibizumab +14).²⁹

The results of the VISTA and VIVID studies demonstrate no difference in visual and anatomic outcomes between the IAI 2q4 and IAI 2q8 dosing regimens, indicating that similar efficacy can be achieved with fewer injections by using the 2q8 dosing regimen. A 2q4 dosing regimen is often difficult to maintain in clinical practice, particularly in a working-age patient population who must miss work because of frequent visits. Therefore, the ability to achieve significant visual improvements with less frequent dosing and visits would be a valuable strategy to manage DME. However, further studies are warranted to determine whether additional extensions in treatment interval beyond 2 months with IAI would be possible in this patient population. Interval extension may be more feasible in DME, in contrast to neovascular age-related macular degeneration, because the disease seems to be self-limiting under adequate therapy.³⁰

Patients with DME are often at higher risk for AEs than nondiabetic individuals because of the presence of systemic comorbidities, such as cardiovascular and renal disease,

and a higher susceptibility to infection.³¹ Thus, repeated intravitreal injections over a prolonged period of time may further increase their cumulative risk of complications.³¹ In VISTA and VIVID, the overall incidence of ocular and nonocular AEs was similar across treatment groups through the second year of treatment. There were no cases of endophthalmitis in any eyes treated with IAI in either study over the course of the 100-week treatment period. Furthermore, the overall rates of Anti-Platelet Trialists' Collaboration—defined arterial thromboembolic events, including vascular deaths, were low and comparable across the treatment groups. Although deaths were more frequent in the IAI groups, the overall rate was low and causes of death were consistent with the underlying disease and comorbidities present in this patient population. Overall, the AE profile over the 100 weeks of the study was consistent with the known safety profile of IAI.

In conclusion, the improvements in visual acuity, DRSS score, and CST achieved at week 52 of the VISTA and VIVID studies with IAI 2q4 and IAI 2q8, compared with macular laser photocoagulation treatment, were sustained at week 100. In addition, the similar efficacy of the IAI 2q4 and IAI 2q8 dosing regimens indicates the potential for a therapeutic option with a longer injection interval and subsequently a reduced number of injections and monitoring visits, a feature that could reduce treatment burden on patients, physicians, and the health care system.

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Abbreviations and Acronyms:

2q4 = 2 mg every 4 weeks; **2q8** = 2 mg every 8 weeks after 5 initial monthly doses; **AE** = adverse event; **aLOCF** = last observation carried forward, including measurements after rescue treatment was given; **BCVA** = best-corrected visual acuity; **CST** = central (optical coherence tomography) subfield thickness; **DME** = diabetic macular edema; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IAI** = intravitreal aflibercept injection; **LOCF** = last observation carried forward, censoring measurements after rescue treatment was given; **NEI VFQ-25** = National Eye Institute Visual Function Questionnaire-25; **OCT** = optical coherence tomography; **SD** = standard deviation; **VEGF** = vascular endothelial growth factor.

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