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Intravitreal Aflibercept for Diabetic Macular Edema

100-Week Results From the VISTA and VIVID Studies

David M. Brown, MD,[1] Ursula Schmidt-Erfurth, MD,[2] Diana V. Do, MD,[3] Frank G. Holz, MD,[4] David S. Boyer, MD,[5] Edoardo Midena, MD,[6] Jeffrey S. Heier, MD,[7] Hiroko Terasaki, MD,[8] Peter K. Kaiser, MD,[9] Dennis M. Marcus, MD,[10] Quan D. Nguyen, MD,[3] Glenn J. Jaffe, MD,[11] Jason S. Slakter, MD,[12] Christian Simader, MD,[2] Yuhwen Soo, PhD,[13] Thomas Schmelter, PhD,[14] George D. Yancopoulos, MD, PhD,[13] Neil Stahl, PhD,[13] Robert Vitti, MD,[13] Alyson J. Berliner, MD, PhD,[13] Oliver Zeitz, MD,[14,15] Carola Metzig, MD,[14] Jean-François Korobelnik, MD[16,17,18]

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;■:1–9 © 2015 by the American Academy of Ophthalmology.*

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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 retinopathy[1] and is characterized by exudation and accumulation of extracellular fluid in the macula[5] 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

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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 μm 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 ± 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 ± SD of 1.6±0.9 and 1.2±0.6 lasers in VISTA, whereas 10 and 15 eyes in VIVID received a mean ± SD of 1.9±1.1 and 1.7±0.8 lasers from week 24 to week 100, respectively.