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Intravitreal Aflibercept for Diabetic Macular Edema

148-Week Results from the VISTA and VIVID Studies

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Purpose: To compare efficacy and safety of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME) over 3 years.

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

Participants: Patients (eyes; n 872) with central-involved DME.

Methods: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control. From week 24, if rescue treatment criteria were met, IAI patients received active laser, and laser control patients received IAI 2q8. From week 100, laser control patients who had not received IAI rescue treatment received IAI as needed per retreatment criteria.

Main Outcome Measures: The primary end point was the change from baseline in best-corrected visual acuity (BCVA) at week 52. We report the 148-week results.

Results: Mean BCVA gain from baseline to week 148 with IAI 2q4, IAI 2q8, and laser control was 10.4, 10.5, and 1.4 letters ($P < 0.0001$) in VISTA and 10.3, 11.7, and 1.6 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained $\geq$15 letters from baseline at week 148 was 42.9%, 35.8%, and 13.6% ($P < 0.0001$) in VISTA and 41.2%, 42.2%, and 18.9% ($P < 0.0001$) in VIVID, respectively. Greater proportions of eyes treated with IAI 2q4 and IAI 2q8 versus those treated with laser control had an improvement of $\geq$2 steps in the Diabetic Retinopathy Severity Scale (DRSS) score in both VISTA (29.9% and 34.4% vs. 20.1% [P 0.0350, IAI 2q4; P 0.0052, IAI 2q8]) and VIVID (44.3% and 47.8% vs. 17.4% [$P < 0.0001$ for both]). In an integrated safety analysis, the most frequent ocular serious adverse event was cataract (3.1%, 2.1%, 0.3% for 2q4, 2q8, and control).

Conclusions: Visual improvements observed with both IAI regimens (over laser control) at weeks 52 and 100 were maintained at week 148, with similar overall efficacy in the IAI 2q4 and IAI 2q8 groups. Treatment with IAI also had positive effects on the DRSS score. Over 148 weeks, the incidence of adverse events was consistent with the known safety profile of IAI. *Ophthalmology 2016;123:2376-2385 © 2016 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

The diabetes mellitus epidemic is growing. According to current predictions, by 2040, approximately 1 in every 10 adults (642 million) worldwide will have the disease.[1] Diabetic retinopathy and associated diabetic macular edema (DME) are serious diabetes mellitus complications and are the leading causes of blindness and visual disability in working-age adults.[2,3]

Current treatment options for DME include macular laser photocoagulation,[4] corticosteroids,[5] and anti-vascular endothelial growth factor (VEGF) agents (i.e., intravitreal aflibercept, ranibizumab, and off-label use of bevacizumab).[6–8] There is a large body of evidence to support anti-VEGF use. Because of superior anatomic and functional outcomes,[6–11] anti-VEGF agents have rapidly replaced macular laser photocoagulation as the standard of care to treat DME.

Aflibercept, a 115-kDA recombinant fusion protein, is composed of the key VEGF binding domains of human VEGF receptors 1 and 2 fused to the constant Fc domain of human immunoglobulin G1,[12] and it binds VEGF-A with high affinity.[13] Unlike ranibizumab and bevacizumab, aflibercept also binds to placental growth factor.[13] Intravitreal aflibercept injection (IAI), which is also known as "VEGF Trap Eye" or "IVT-AFL" in the scientific literature, is currently indicated to treat neovascular age-related macular degeneration (AMD), macular edema

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Table 1. Treatment Experience from Baseline to Week 148

	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 through week 148, mean (SD)						
Macular laser photocoagulation	3.8 (2.4)	–	–	2.6 (2.0)	–	–
Intravitreal aflibercept	–	29.6 (9.8)	18.1 (4.8)	–	32.0 (9.7)	18.1 (5.1)
Study eyes that received rescue treatment* from week 24 to week 148, n (%)	63 (40.9)*	7 (4.5)*	16 (10.5)*	47 (35.3)*	10 (7.4)*	16 (11.9)*
Mean (SD) No. of rescue treatment	13.5 (3.9)	1.4 (0.8)	1.4 (1.1)	13.5 (4.3)	2.3 (1.5)	1.9 (1.0)
Laser control eyes that received rescue or PRN† IAI treatment from week 24 to week 148, n (%)	134 (87.0)	–	–	109 (82.0)	–	–
Mean (SD) number of IAI injections	9.8 (5.0)	–	–	9.3 (5.2)	–	–

– = not applicable; IAI = intravitreal aflibercept injection; PRN = pro re nata; SD = standard deviation; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses.
Safety analysis set.
*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.
†Laser control patients who did not meet criteria for rescue treatment during weeks 24 to 96 received IAI 2 mg PRN per the prespecified retreatment criteria from week 100 to week 144. In VISTA and VIVID, respectively, 71 and 64 laser control patients received a mean (SD) of 6.5±3.2 and 6.0±3.3 PRN IAI injections from week 100 to week 148.

secondary to retinal vein occlusion, myopic choroidal neovascularization, and DME. Intravitreal aflibercept injection is approved for the treatment of DME in the United States, the European Union, Australia, and Japan.

The efficacy and safety of IAI in DME have been demonstrated over 2 years in the VISTA^{DME} and VIVID^{DME} studies.[7,14] Both trials showed that, after 52 and 100 weeks of treatment, IAI provides significantly greater improvements in both functional and anatomic outcomes when compared with macular laser photocoagulation.[7,14] In addition, the proportion of eyes with ≥2-step improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) score was significantly greater with IAI than with laser control, suggesting a beneficial effect on the underlying diabetic retinopathy.[7,14] We report the 148-week results of the VISTA and VIVID 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.[7,14] Each clinical site's respective institutional review board or 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.[15,16] Data for this report, which present the 148-week results, were collected between May 2011 and March 2015.

Patient eligibility for the VISTA and VIVID studies has been described.[14] Briefly, adult patients with type 1 or 2 diabetes mellitus who presented with central-involved DME (defined as retinal thickening involving the central 1-mm subfield [central subfield thickness {CST}] as determined by spectral domain optical coherence tomography [SD OCT]) were eligible for enrollment if best-corrected visual acuity (BCVA) was between 73 and 24 letters (20/40 to 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 3 groups to receive 1 of the following treatments (a) 2 mg IAI every 4 weeks (2q4), (b) 2 mg IAI every 8 weeks after 5 initial monthly doses (2q8), and (c) macular laser photocoagulation at baseline. Treatments continued through week 148.

Beginning at week 12, study eyes in all treatment groups were assessed for laser retreatment. 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 IAI 2q4 and IAI 2q8 groups received sham laser and those in the laser group received active laser, but no more frequently than every 12 weeks.

Beginning at week 24, study eyes in all treatment groups also could receive additional (rescue) treatment if DME worsened, as defined by a ≥10-letter loss at 2 consecutive visits or ≥15-letter loss at 1 visit from the best previous measurement, when BCVA was not better than baseline. When these criteria were met, study eyes in the IAI 2q4 and IAI 2q8 groups could receive active laser (rather than sham laser) from week 24 onward and continued with the existing IAI regimen; study eyes in the laser control group received 5 doses of 2 mg IAI every 4 weeks followed by dosing every 8 weeks until the end of the study (rather than sham injections), in addition to laser, when the laser retreatment criteria were met. Patients could receive both laser and IAI, when applicable, at the same visit.

Beginning at week 100, patients in the laser control group who did not meet criteria for rescue treatment during weeks 24 to 96

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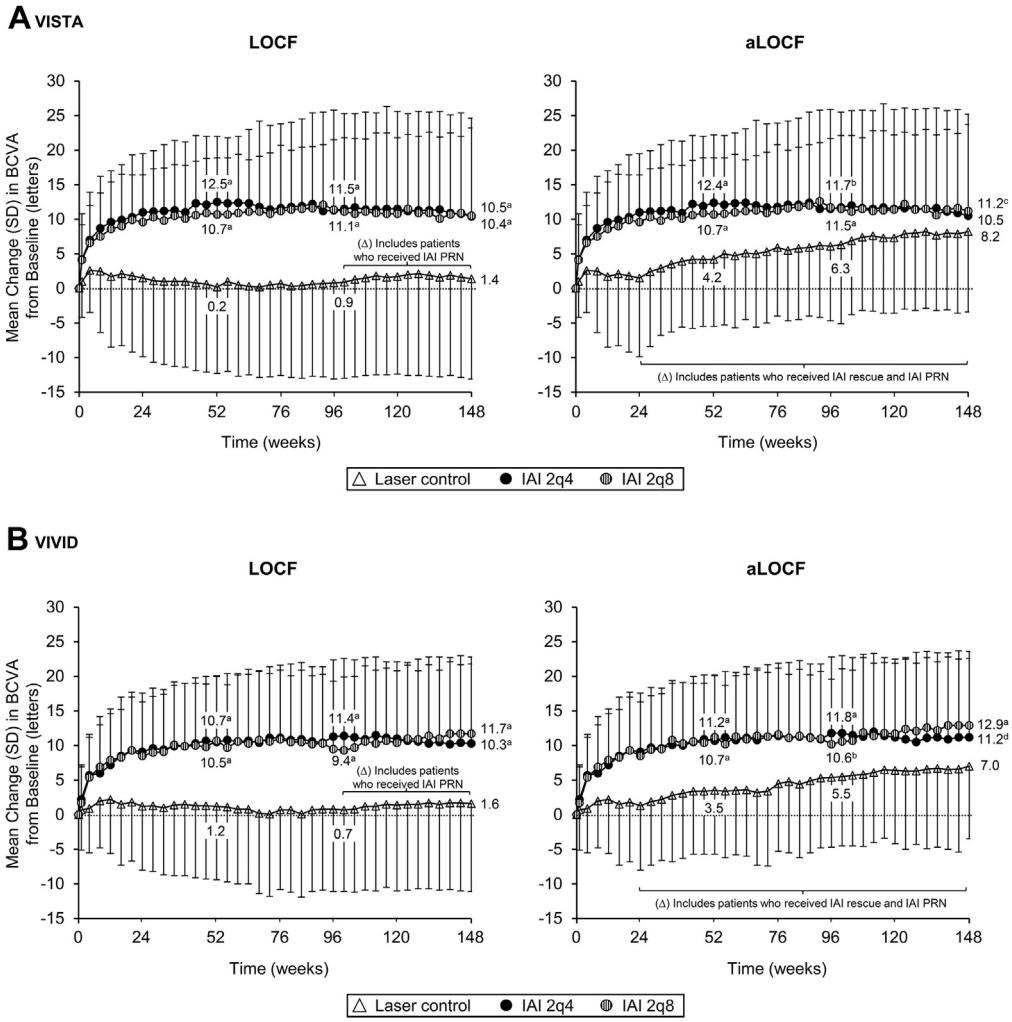

Figure 1. Mean (±standard deviation) change in best-corrected visual acuity (BCVA) from baseline through week 148 in VISTA (**A**) and VIVID (**B**). Primary analysis method (LOCF): last observation carried forward, censoring measurements after rescue treatment was given; measurements after as needed (PRN) treatment was given were not censored. Ancillary analysis method (aLOCF): last observation carried forward, including measurements after additional or PRN treatment was given. Full analysis set. In VISTA, n = 154 for laser control, n = 154 for intravitreal aflibercept injection (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. $^{a}P < 0.0001$, $^{b}P = 0.0002$, $^{c}P = 0.0345$, and $^{d}P = 0.0021$ versus laser control from the analysis of covariance. aLOCF = last observation carried forward, including measurements after additional or pro re nata (PRN) treatment was given; LOCF = last observation carried forward, censoring measurements after rescue treatment was given; measurements after PRN treatment was given were not censored; SD = standard deviation; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses.

received 2 mg IAI as needed (pro re nata [PRN]) when any 1 of the following criteria was met: a >50 μm increase in CST compared with the lowest previous measurement; (b) new or persistent cystic retinal changes or subretinal fluid on optical coherence tomography (OCT), or persistent diffuse edema in the central subfield on OCT; (c) a loss of ≥5 letters in BCVA from the best previous measurement in conjunction with any increase in CST; or (d) an increase of ≥5 letters in BCVA between the current and the most recent visit.

Outcome Measures

The primary efficacy end point, change from baseline BCVA in ETDRS letters at week 52, and the prespecified secondary and exploratory efficacy end points at week 52 and week 100 have been reported.[7,14] We report the 148-week results of the VISTA and VIVID studies. Prespecified efficacy end points at week 148 were exploratory and included the change from baseline in BCVA, proportion of eyes that gained or lost ≥10 and ≥15 letters from baseline, proportion of eyes with a ≥2-step improvement from baseline in the DRSS score,[17] and change from baseline in CST as determined by SD OCT.

The BCVA using the ETDRS protocol[4] and CST using SD OCT were assessed every 4 weeks. Color fundus photography was performed at baseline and weeks 24, 52, 72, 100, 124, and 148. Masked readers at independent central reading centers evaluated OCT images for CST (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).

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Table 2. Eyes with Vision Gains and Losses from Baseline at Week 148 in VISTA

	LOCF				aLOCF			
	Laser Control (n = 154)	*IAI 2q4 (n = 154)*	*IAI 2q8 (n = 151)*	P *Value*	*Laser Control (n = 154)*	*IAI 2q4 (n = 154)*	*IAI 2q8 (n = 151)*	P *Value*
Vision gain, n (%)								
≥15 letters	21 (13.6)	66 (42.9)	54 (35.8)	<0.0001*	37 (24.0)	68 (44.2)	58 (38.4)	0.0002† 0.0069‡
≥10 letters	48 (31.2)	90 (58.4)	89 (58.9)	<0.0001*	74 (48.1)	92 (59.7)	93 (61.6)	0.0291† 0.0177‡
Vision loss, n (%)								
≥10 letters	30 (19.5)	9 (5.8)	5 (3.3)	0.0004† <0.0001‡	8 (5.2)	10 (6.5)	4 (2.6)	0.6032† 0.2531‡
≥15 letters	15 (9.7)	6 (3.9)	4 (2.6)	0.0386† 0.0107‡	7 (4.5)	7 (4.5)	4 (2.6)	0.9884† 0.3753‡

aLOCF = ancillary last observation carried forward, including measurements after additional or as needed (PRN) treatment was given; IAI = intravitreal aflibercept injection; LOCF = last observation carried forward, censoring measurements after rescue treatment was given; measurements after PRN treatment was given were not censored; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses.
Full analysis set.
*For both IAI 2q4 and 2q8 compared with laser control.
†For IAI 2q4 compared with laser control.
‡For IAI 2q8 compared with laser control.

Statistical Analyses

All outcome measures at week 148 were analyzed in an exploratory manner, and *P* values reported are considered nominal (not prespecified). 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 postbaseline 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 (primary analysis method; LOCF). Measurements obtained after PRN IAI treatment in the laser group were not censored. Prespecified sensitivity analyses were also performed to include values after rescue treatment was given (ancillary analysis method; aLOCF). Safety was assessed on the integrated safety set from VISTA and VIVID, including all randomized patients who received any study treatment.

Table 3. Eyes With Vision Gains and Losses from Baseline at Week 148 in VIVID

	LOCF				aLOCF			
	Laser Control (n = 132)	*IAI 2q4 (n = 136)*	*IAI 2q8 (n = 135)*	P *Value*	*Laser Control (n = 132)*	*IAI 2q4 (n = 136)*	*IAI 2q8 (n = 135)*	P *Value*
Vision gain, n (%)								
≥15 letters	25 (18.9)	56 (41.2)	57 (42.2)	<0.0001*	30 (22.7)	63 (46.3)	60 (44.4)	<0.0001† 0.0001‡
≥10 letters	39 (29.5)	76 (55.9)	76 (56.3)	<0.0001*	55 (41.7)	83 (61.0)	83 (61.5)	0.0013† 0.0010‡
Vision loss, n (%)								
≥10 letters	26 (19.7)	5 (3.7)	3 (2.2)	<0.0001*	8 (6.1)	5 (3.7)	2 (1.5)	0.3651† 0.0498‡
≥15 letters	18 (13.6)	4 (2.9)	0 (0)	0.0013† <0.0001‡	6 (4.5)	4 (2.9)	1 (0.7)	0.4900† 0.0530‡

aLOCF = ancillary last observation carried forward, including measurements after additional or PRN treatment was given; IAI = intravitreal aflibercept injection; LOCF = last observation carried forward, censoring measurements after rescue treatment was given; measurements after PRN treatment was given were not censored; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses.
Full analysis set.
*For both IAI 2q4 and 2q8 compared with laser control.
†For IAI 2q4 compared with laser control.
‡For IAI 2q8 compared with laser control.

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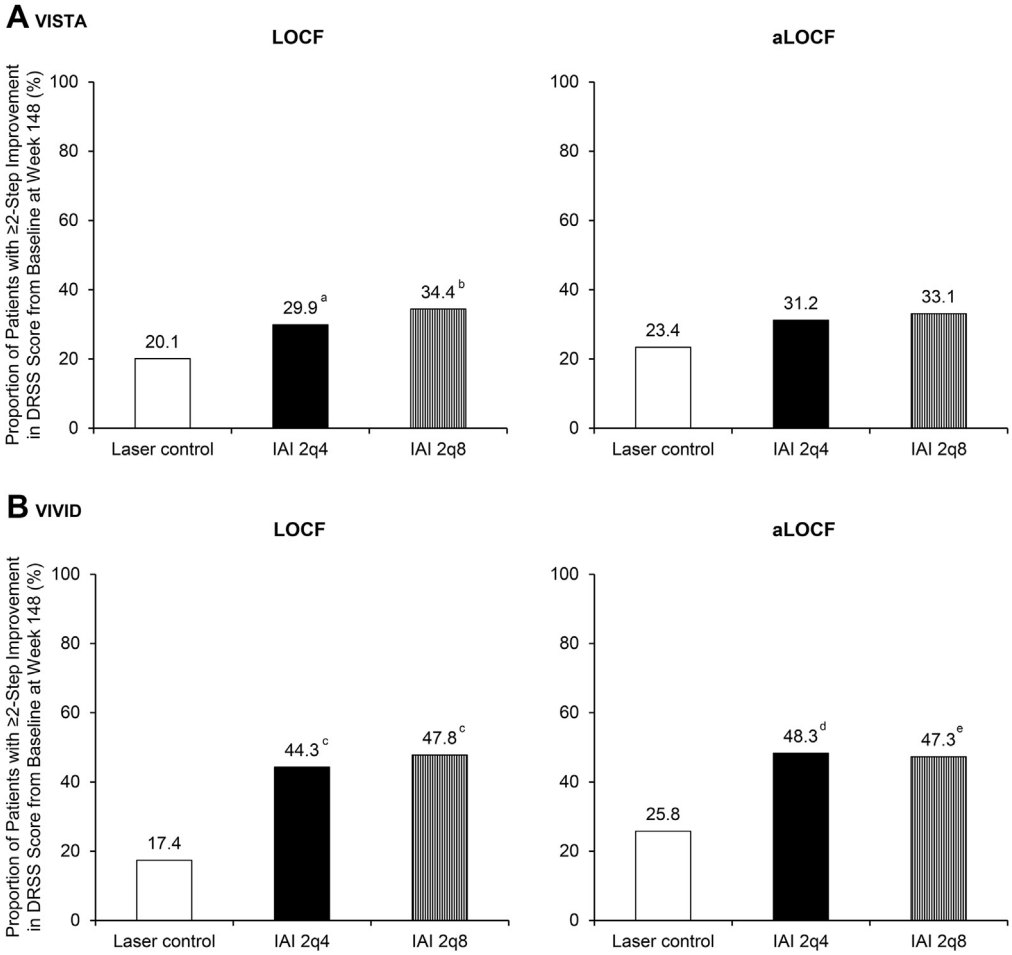

Figure 2. Proportion of eyes with a ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score from baseline at week 148 in VISTA (**A**) and VIVID (**B**). Primary analysis method (LOCF): last observation carried forward, censoring measurements after rescue treatment was given; measurements after as needed (PRN) treatment was given were not censored. Ancillary analysis method (aLOCF): last observation carried forward, including measurements after additional or PRN treatment was given. In VISTA, analyses were performed using the full analysis set. 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, LOCF: n = 86 for laser control, n = 88 for IAI 2q4, and n = 92 for IAI 2q8; aLOCF: n = 89 for laser control, n = 89 for IAI 2q4, and n = 93 for IAI 2q8. [a]$P = 0.0350$, [b]$P = 0.0052$, [c]$P < 0.0001$, [d]$P < 0.0016$, and [e]$P < 0.0022$ versus laser control. aLOCF = last observation carried forward, including measurements after additional or PRN treatment was given; LOCF = last observation carried forward, censoring measurements after rescue treatment was given; measurements after PRN treatment was given were not censored; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses.

Results

Patient Disposition and Treatment Experience

VISTA treated 461 eyes, and VIVID treated 404 eyes (Appendix 1, available at www.aaojournal.org). Demographics and baseline characteristics of patients were reported by Korobelnik et al.[14] Overall, 76.6% of eyes in VISTA and 74.4% of eyes in VIVID completed the study through week 148 (Appendix 1, available at www.aaojournal.org). The most common reason for discontinuation during year 3 was withdrawal by patient in both VISTA and VIVID, with other common reasons being death and adverse events (Appendix 1, available at www.aaojournal.org). From baseline to week 148, study eyes in the IAI 2q4 and IAI 2q8 groups received a mean of 29.6 and 18.1 injections in VISTA and 32.0 and 18.1 injections in VIVID, respectively (Table 1). Eyes in the laser control group received an average of 3.8 and 2.6 laser treatments in VISTA and VIVID, respectively. From week 24 to week 148, rescue treatment in VISTA was given to 4.5% and 10.5% of eyes in the IAI 2q4 and IAI 2q8 groups compared with 40.9% of eyes in the laser control group, and in VIVID to 7.4% and 11.9% of eyes in the IAI 2q4 and IAI 2q8 groups compared with 35.3% of eyes in the laser control group, respectively (Table 1). Considering PRN IAI treatment given from week 100 to week 148, 87.0% of laser control eyes in VISTA and 82.0% of laser control eyes in VIVID received IAI treatment (rescue or PRN) from week 24 to week 148 (Table 1).

Efficacy Outcomes

In both VISTA and VIVID, eyes with DME treated with IAI 2q4 and IAI 2q8 demonstrated sustained visual acuity gains through week 148. With the primary analysis method (LOCF), which censored measurements after rescue treatment was given, but included measurements after PRN treatment, the mean ± standard

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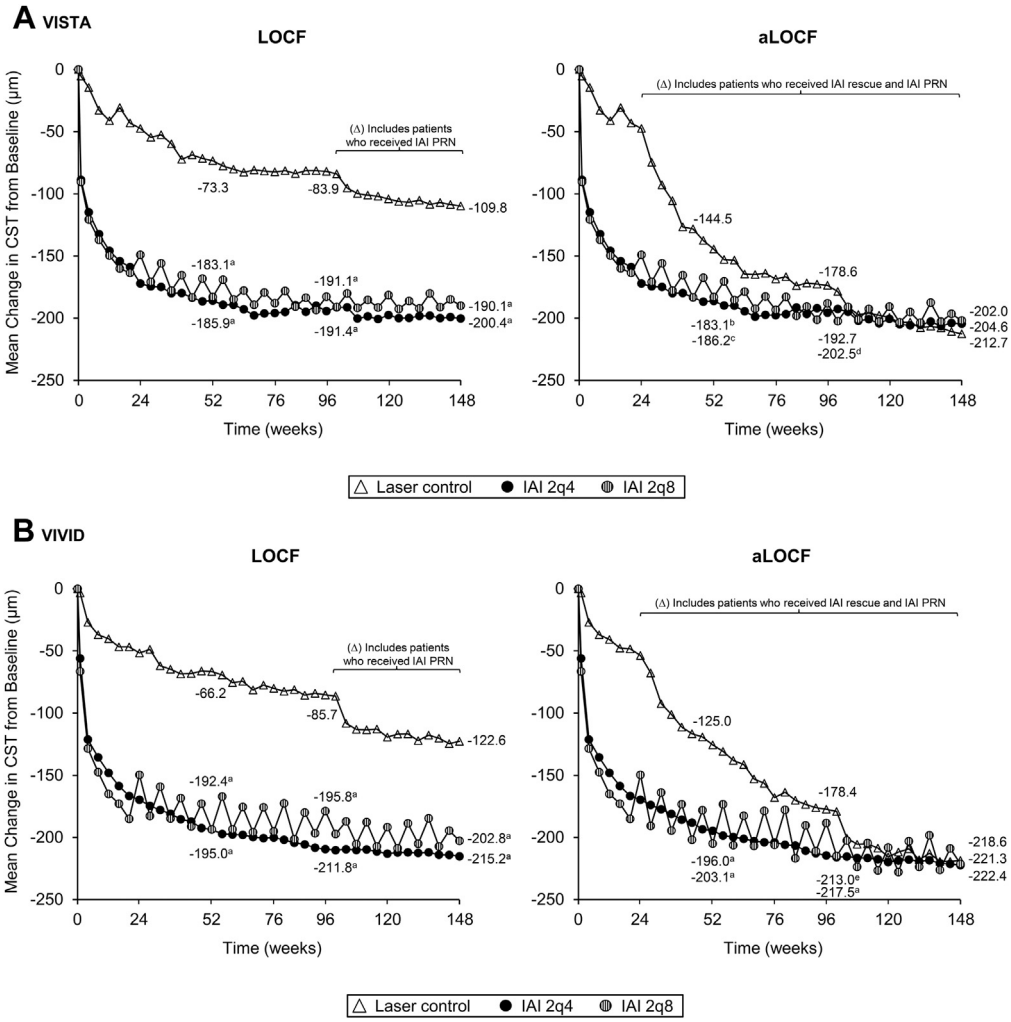

Figure 3. Mean change in central subfield thickness (CST) from baseline to week 148 in VISTA (**A**) and VIVID (**B**). Primary analysis method (LOCF): last observation carried forward, censoring measurements after rescue treatment was given; measurements after as needed (PRN) treatment was given were not censored. Ancillary analysis method (aLOCF): last observation carried forward, including measurements after additional or PRN treatment was given. Full analysis set. In VISTA, n = 154 for laser control, n = 154 for intravitreal aflibercept injection (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]$P < 0.0001$, [b]$P = 0.0001$, [c]$P = 0.0003$, [d]$P < 0.0033$, and [e]$P = 0.0002$ versus laser control. aLOCF = last observation carried forward, including measurements after additional or PRN treatment was given; DRSS = Diabetic Retinopathy Severity Scale; LOCF = last observation carried forward, censoring measurements after rescue treatment was given; measurements after PRN treatment was given were not censored; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses; IAI = intravitreal aflibercept injection.

deviation change from baseline BCVA in the IAI 2q4 and IAI 2q8 groups at week 148 was +10.4±14.2 and +10.5±12.7 letters versus +1.4±14.5 letters in the laser control group ($P < 0.0001$ for both IAI groups compared with laser control) in VISTA, and +10.3±12.5 and +11.7±10.1 letters versus +1.6±12.7 letters ($P < 0.0001$ for both IAI groups compared with laser control) in VIVID (Fig 1), respectively. With the ancillary analysis method (aLOCF), which included values after all IAI treatments (rescue or PRN), the between-group differences narrowed, but remained numerically (VISTA) and statistically (VIVID) in favor of the IAI groups (Fig 1).

In both VISTA and VIVID, more eyes treated with IAI gained ≥10 and ≥15 letters, whereas more eyes treated with laser control lost ≥10 and ≥15 letters from baseline at week 148 using the primary analysis method (LOCF) (Tables 2 and 3). The between-group differences in the proportions of patients who gained ≥15 letters narrowed, but remained in favor of the IAI groups when measurements after all IAI treatments (rescue or PRN) were included in the analyses (aLOCF, Tables 2 and 3).

With the primary analysis method (LOCF), higher proportions of eyes treated with IAI 2q4 and IAI 2q8 compared with those treated with laser control had at least a ≥2-step improvement in the DRSS score in both VISTA and VIVID (Fig 2). The between-group differences narrowed, but remained numerically in favor of the IAI groups when measurements after all IAI treatments (rescue or PRN) were included in the analyses (aLOCF) (Fig 2).

With the primary analysis method (LOCF), the improvements from baseline CST in the IAI 2q4 and IAI 2q8 groups were robust throughout the study and significantly greater than those seen in the laser control group at week 148 in both VISTA and VIVID (Fig 3). The between-group differences at week 148 disappeared when measurements after all IAI treatments (rescue or PRN) were included in the analyses (aLOCF) (Fig 3).

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Table 4. Ocular Serious Adverse Events from Baseline to Week 148

	Control (n = 287)	IAI 2q4 (n = 291)	IAI 2q8 (n = 287)	All IAI (n = 578)
Any ocular SAEs in study eye, n (%)	18 (6.3)	25 (8.6)	18 (6.3)	43 (7.4)
Cataract	1 (0.3)	9 (3.1)	6 (2.1)	15 (2.6)
Cataract subcapsular	1 (0.3)	0	2 (0.7)	2 (0.3)
Corneal epithelium defect	1 (0.3)	0	0	0
Diabetic retinal edema	0	1 (0.3)	0	1 (0.2)
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	3 (1.0)	2 (0.7)	5 (0.9)
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)	2 (0.7)	0	2 (0.3)
Visual acuity reduced	0	1 (0.3)	1 (0.3)	2 (0.3)
Vitreous hemorrhage	5 (1.7)	4 (1.4)	3 (1.0)	7 (1.2)
Injection site injury	0	1 (0.3)	0	1 (0.2)
Endophthalmitis	0	2 (0.7)	1 (0.3)	3 (0.5)
Intraocular pressure increased	0	0	1 (0.3)	1 (0.2)
Visual acuity tests abnormal	1 (0.3)	0	0	0
Visual field defect	0	0	1 (0.3)	1 (0.2)
Cataract operation	2 (0.7)	2 (0.7)	1 (0.3)	3 (0.5)

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

Adverse Events

There were no clinically relevant differences in pattern or frequency of ocular serious adverse events (SAEs) between the treatment groups (Table 4). Study eye endophthalmitis was reported in 3 eyes in total: 2 eyes (0.7%) in the IAI 2q4 group and 1 eye (0.3%) in the IAI 2q8 group. The incidence of nonocular SAEs was slightly higher for some events in the combined IAI group (e.g., anemia, coronary artery disease, and cerebrovascular accident) and for others in the control group (e.g., acute myocardial infarction and hyperkalemia) (Appendix 2, available at www.aaojournal.org). The overall incidences of arterial thromboembolic events defined by the Anti-Platelet Trialists' Collaboration criteria were 10.7%, 7.3%, and 7.7% in the IAI 2q4, IAI 2q8, and control groups, respectively (Table 5). The incidences of death in the IAI 2q4, IAI 2q8, and control groups were 7.7%, 3.9%, and 3.2% in VISTA, 5.1%, 5.2%, and 2.3% in VIVID, and 6.5%, 4.5%, and 2.8% in the integrated dataset, respectively. A listing of causes of death is shown in Appendix 2 (available at www.aaojournal.org).

Discussion

In the VISTA and VIVID trials, eyes treated with IAI 2q4 and IAI 2q8 achieved significantly greater improvements in functional and anatomic outcomes when compared with laser control at both weeks 52 and 100. The improvements observed at 100 weeks[7] were maintained over 148 weeks of treatment. In both studies, based on the primary analysis method LOCF (i.e., censoring measurements after rescue treatment was given and including measurements in the laser control group after IAI PRN treatment), mean BCVA changes from baseline to week 148 were significantly greater in eyes treated with IAI 2q4 and IAI 2q8 compared with laser control. In addition, a significantly

Table 5. Anti-Platelet Trialists' Collaboration—Defined Arterial Thromboembolic Events from Baseline to Week 148

	Control (n = 287)	IAI 2q4 (n = 291)	IAI 2q8 (n = 287)	All IAI (n = 578)
Any APTC-ATEs,* n (%)	22 (7.7)	31 (10.7)	21 (7.3)	52 (9.0)
Nonfatal myocardial infarction	9 (3.1)	10 (3.4)	9 (3.1)	19 (3.3)
Nonfatal stroke	10 (3.5)	11 (3.8)	7 (2.4)	18 (3.1)
Vascular death	4 (1.4)	11 (3.8)	6 (2.1)	17 (2.9)

APTC-ATEs = Anti-Platelet Trialists' Collaboration—defined arterial thromboembolic events; IAI = intravitreal aflibercept injection; 2q4 = 2 mg IAI every 4 weeks; 2q8 = 2 mg IAI every 8 weeks after 5 initial monthly doses.
Integrated safety analysis set.
*Adjudicated by a masked committee.

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greater proportion of IAI-treated eyes gained ≥10 and ≥15 letters at week 148.

We found that a significantly greater proportion of eyes treated with IAI 2q4 and IAI 2q8 had an improvement of ≥2 steps in the DRSS score compared with eyes treated with laser control. These data support previous observations that IAI may promote regression of the underlying diabetic retinopathy beyond the macular area.[7,14]

Improvements from baseline CST also were significantly greater in the IAI 2q4 and IAI 2q8 groups compared with the laser control group at week 148 in both studies, and there was no evidence that the observed fluctuations in CST in the IAI 2q8 group were associated with any limitation in visual acuity benefit over the 148 weeks of follow-up.

On average, the IAI 2q8 regimen provided visual and anatomic improvements similar to those achieved by the IAI 2q4 regimen through week 148 with substantially fewer injections. This ability to achieve equivalent visual and anatomic benefits with less frequent dosing supports the potential for reduced treatment burden, including fewer clinic visits, for these patients. However, because of the spectrum of disease severity, there may be patients with DME who would benefit from more frequent treatment, as it has been shown for a subpopulation of patients with AMD.[18] Further analysis is warranted to identify these patients.

With the ancillary analysis method (aLOCF) (i.e., including values after all IAI treatments [rescue or PRN]), between-group differences narrowed, but remained in favor of IAI 2q4 and IAI 2q8 for visual end points when compared with laser control. However, between-group differences in CST completely disappeared by week 148. These findings were expected because a large number of laser control patients (>80%) received IAI treatment as rescue beginning at week 24 or as PRN starting at week 100. Of note, the catch-up with visual and anatomic improvements after delayed treatment with IAI was more pronounced than those seen in prior trials with ranibizumab.[19] The remaining between-group differences in visual outcomes between the laser and IAI groups are not reflective of anatomic improvements (because these were similar across treatment groups at week 148), indicating there may be irreversible vision losses because of delayed treatment with IAI in the laser control group.

The presence of underlying systemic comorbidities in patients with DME can put them at a potentially high risk for adverse events, and repeated intravitreal injections over a prolonged period of time may increase their cumulative risk of complications.[20] In both VISTA and VIVID, the overall incidences of ocular and nonocular SAEs were similar across treatment groups through 148 weeks of treatment. The overall rates of Anti-Platelet Trialists' Collaboration—defined arterial thromboembolic events 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. In general, even with a longer treatment period, no new safety signals were observed, and the adverse event profile of IAI over the 148 weeks of the study was consistent with the known safety profile of IAI.[21]

In conclusion, visual acuity improvements observed with both IAI regimens (over laser control) at weeks 52 and 100 were maintained at week 148. Because the IAI 2q4 and IAI 2q8 regimens had similar efficacy, the IAI 2q8 regimen may potentially reduce the treatment burden of anti-VEGF therapy to manage most patients with DME.

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References

1. International Diabetes Foundation. IDF Diabetes Atlas. http://www.diabetesatlas.org/key-messages.html. Accessed January 2016.
2. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. N Engl J Med 2012;366:1227 39.
3. Boyer DS, Hopkins JJ, Sorof J, Ehrlich JS. Anti-vascular endothelial growth factor therapy for diabetic macular edema. Ther Adv Endocrinol Metab 2013;4:151 69.
4. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985;103:1796 806.
5. Ciulla TA, Harris A, McIntyre N, Jonescu-Cuypers C. Treatment of diabetic macular edema with sustained-release glucocorticoids: intravitreal triamcinolone acetonide, dexamethasone implant, and fluocinolone acetonide implant. Expert Opin Pharmacother 2014;15:953 9.
6. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789 801.
7. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology 2015;122:2044 52.
8. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Arch Ophthalmol 2012;130:972 9.
9. Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. Ophthalmology 2012;119:2312 8.
10. Nepomuceno AB, Takaki E, Paes de Almeida FP, et al. A prospective randomized trial of intravitreal bevacizumab versus ranibizumab for the management of diabetic macular edema. Am J Ophthalmol 2013;156:502 510.e2.
11. Schmidt-Erfurth U, Lang GE, Holz FG, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. Ophthalmology 2014;121:1045 53.
12. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A 2002;99:11393 8.

Samsung et al. v. Regeneron IPR2023-00884
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13. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis 2012;15:171 85.
14. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology 2014;121:2247 54.
15. ICH Harmonized Tripartite Guideline. Guideline for Good Clinical Practice; 1996. Available at: http://www.nhrec.org.za/docs/trainingrequirements/ICHGCP.pdf. Accessed August 30, 2016.
16. U.S. Government Printing Office. Health Insurance Portability and Accountability Act of 1996. Available at: http://www.gpo.gov/fdsys/pkg/PLAW-104publ191/html/PLAW-104publ191.htm. Accessed August 30, 2016.
17. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98:823 33.
18. Jaffe GJ, Kaiser PK, Thompson D, et al. Differential response to anti-VEGF regimens in age-related macular degeneration patients with early persistent retinal fluid. Ophthalmology 2016;123:1856 64.
19. Brown DM, Nguyen QD, Marcus DM, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120:2013 22.
20. Shikari H, Silva PS, Sun JK. Complications of intravitreal injections in patients with diabetes. Semin Ophthalmol 2014;29:276 89.
21. Kitchens JW, Do DV, Boyer DS, et al. Comprehensive review of ocular and systemic safety events with intravitreal aflibercept injection in randomized controlled trials. Ophthalmology 2016;123:1511 20.

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Abbreviations and Acronyms:
aLOCF = last observation carried forward, including measurements after additional or PRN treatment was given; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CST** = central 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, measurements after PRN treatment was given were not censored; **OCT** = optical coherence tomography; **PRN** = pro re nata; **SAE** = serious adverse event; **SD-OCT** = spectral domain optical coherence tomography; **VEGF** = vascular endothelial growth factor; **2q4** = 2 mg every 4 weeks; **2q8** = 2 mg every 8 weeks after 5 monthly doses.

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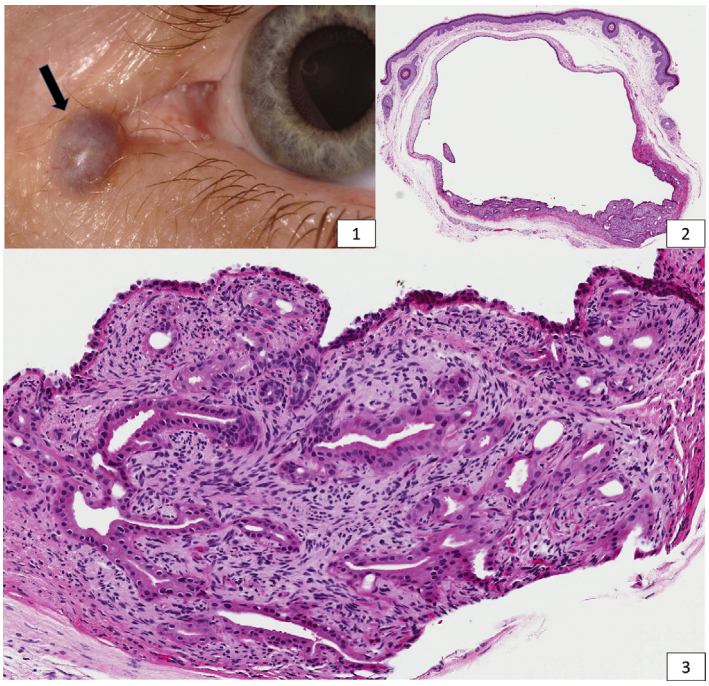
Pictures & Perspectives



Tubular Apocrine Adenoma in Association with an Apocrine Hidrocystoma

A 42-year-old man presented with a left medial commissure lesion that progressed in size and pigmentation over 8 years (Fig 1, *arrow*). Clinically, the lesion appeared gray in color and mild telangiectatic vessels were seen. Histopathology revealed a large apocrine hidrocystoma with a circumscribed nodule composed of variably sized tubules adjacent to the cyst wall (Fig 2). The cells displayed abundant eosinophilic cytoplasm, uniform round nuclei, and apocrine snouting (Fig 3). Tubular apocrine adenomas are rare benign tumors with a predominance in females (2:1), and are most commonly seen on the scalp, cheek, axilla, and breast.

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