MODULE 10.11
Clinical Studies and Treatment Data - VIVID and VISTA

VIVID and VISTA[1]

Study Name	Intravitreal aflibercept for diabetic macular edema
Purpose of study	To directly compare aflibercept (anti–vascular endothelial growth factor [anti-VEGF]) to laser treatment in diabetic macular edema (DME)
Study authors	Korobelnik JF, Do DV, Schmidt-Erfurth U, et al.
Published in	*Ophthalmology.* 2014;121:2247-2254.
Study also known as	VIVID/VISTA
Subsequent studies	None

Study Overview

Aflibercept is a fusion protein designed to inhibit VEGF-A and placental growth factor (PlGF).[1] Based on promising results from the phase 2 DaVINCI studies,[2] the VIVIDDME and VISTADME studies (hereafter referred to as "VIVID" or "VISTA" were initiated and served as the pivotal phase 3 trials used as the basis for global regulatory submissions. Both studies are visualized at the end of this module.

VIVID and VISTA are 2 similarly designed, phase 3, randomized, double-masked, active-controlled, 148-week trials. VISTA was conducted in 54 centers (461 patients) in the US, whereas VIVID was conducted in Europe, Australia, and Japan (73 centers, 404 patients).[3] Published results are only available for the preliminary 52 weeks.[3] Baseline characteristics and demographics were similar between the 2 studies; the notable exception was that VISTA included a greater proportion of black patients, and VIVID had a greater proportion of Asian patients. Significantly more eyes in VIVID had previously undergone anti-VEGF therapy compared to eyes in VISTA (42.9% vs 8.9%, respectively.)[3]

The primary endpoint was the mean change in best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline to week 52, and notable secondary endpoints included the proportion of eyes that gained ≥ 10 letters and ≥ 15 letters from baseline to week 52, the proportion of eyes with at least a 2-step improvement in the ETDRS Diabetic Retinopathy Severity Scale, change in central subfield thickness (CST) from baseline to week 52 (determined by optical coherence tomography [OCT]), and mean number of injections and laser procedures.

The 2 studies enrolled a total of 872 participants with central DME involvement (retinal thickening involving the 1-mm CST). The BCVA was between 73 and 24 letters (20/40 to 20/320 Snellen equivalent) in the study eye.[3]

Eyes were randomized in a 1:1:1 ratio to receive 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 once at baseline and sham injections at every visit (laser control group). Eyes in all 3 groups were assessed for laser retreatment beginning at week 12 per ETDRS criteria and would receive sham (2q4 or 2q8) or active laser (laser group) as needed. Beginning week 24, all groups could receive additional (rescue) treatment if ≥ 15 letters were lost at any single visit due to DME progression or ≥ 10 letters were lost on 2 consecutive visits, and if BCVA diminished since baseline. If study eyes met the rescue treatment criteria, 2q4 and 2q8 eyes then received active laser instead of sham from week 24 onward, and eyes in the laser group received 5 doses of 2 mg IAI every 4 weeks followed by dosing every 8 weeks.[3]

In VISTA, patients in the laser arm received a mean of 2.7 active macular laser photocoagulation treatments. Patients in the IAI arms received a mean of 11.8 and 8.4 active injections in the 2q4 and 2q8 groups, respectively. In VIVID, patients in the laser arm received a mean of 2.1 active macular laser photocoagulation treatments. Patients in the IAI arms received a mean of 12.2 and 8.7 active injections in the 2q4 and 2q8 groups, respectively, over 52 weeks. Rescue treatment was necessary in VISTA in 31.2% of patients in the macular laser photocoagulation arm,

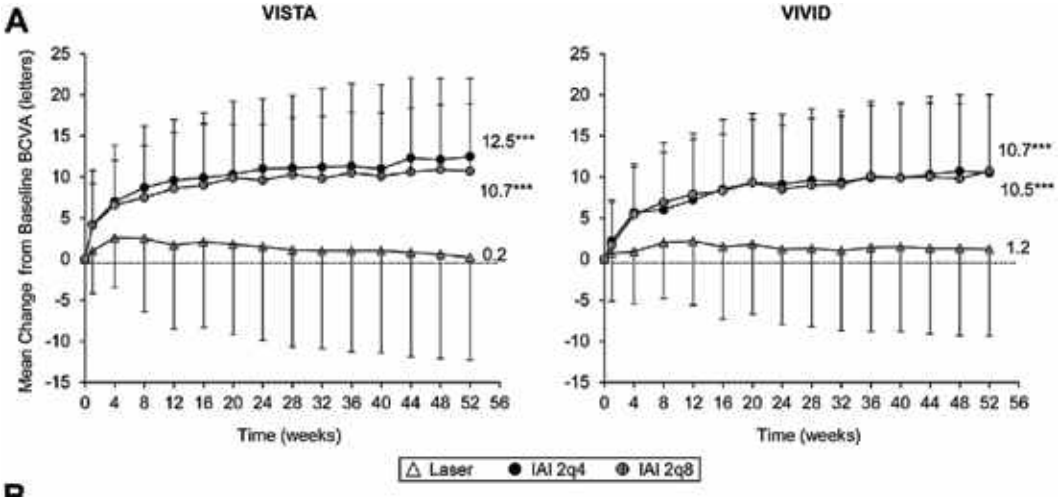


Figure 1: Mean change in BCVA from baseline to week 52.

2.6% of patients in the IAI 2q4 arm, and 0.7% of patients in the IAI 2q8 arm. In VIVID, 24.1% of patients in the macular laser photocoagulation arm, 4.4% of patients in the IAI 2q4 arm, and 8.1% of patients in the IAI 2q8 arm received rescue treatment at 52 weeks.

In both studies, eyes treated with IAI had significant BCVA gains from baseline when compared to laser.[3] 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 ($P < .0001$) in VISTA, and 10.5 ± 9.5 letters and 10.7 ± 9.3 letters versus 1.2 ± 10.6 letters ($P < .0001$) in VIVID, respectively (see Figure 1). In all secondary endpoints, patients in the IAI arms had better outcomes than those in the laser arms.[3]

In general, the improvements from baseline in CST were significantly greater at week 52 in the IAI 2q4 and 2q8 groups compared with the macular laser photocoagulation group in both the VISTA study (–186 µm and –183 µm vs –73 µm, respectively) and the VIVID study (–195 µm and –192 µm vs –66 µm, respectively)[3] (see Figure 2).

Finally, arterial thromboembolic events and deaths were not notably different between arms; no death was associated with the study drug or the laser treatment. No cases of endophthalmitis were reported in either study, and rates of intraocular inflammation were similar across all arms in both studies as well.

Study Implications

These were the first phase 3 studies to compare VEGF-blockade alone directly with laser alone in patients with DME. Patients in the 2q8 arm were dose-loaded with 5 monthly injections before continuing onto the 8-week dosing regimen. This was also the first study to allow a fellow eye to receive anti-VEGF treatment with either IAI or another anti-VEGF. Although unlikely, it is not clear if there may have been a systemic effect with anti-VEGF treatment of the fellow eye in the study eye.

This was also the first study to use 52-week endpoints instead of the more traditional 104-weeks. According to the study authors and others, 1-year outcomes with anti-VEGF agents in DME are largely maintained in years 2 and 3.[4-7]

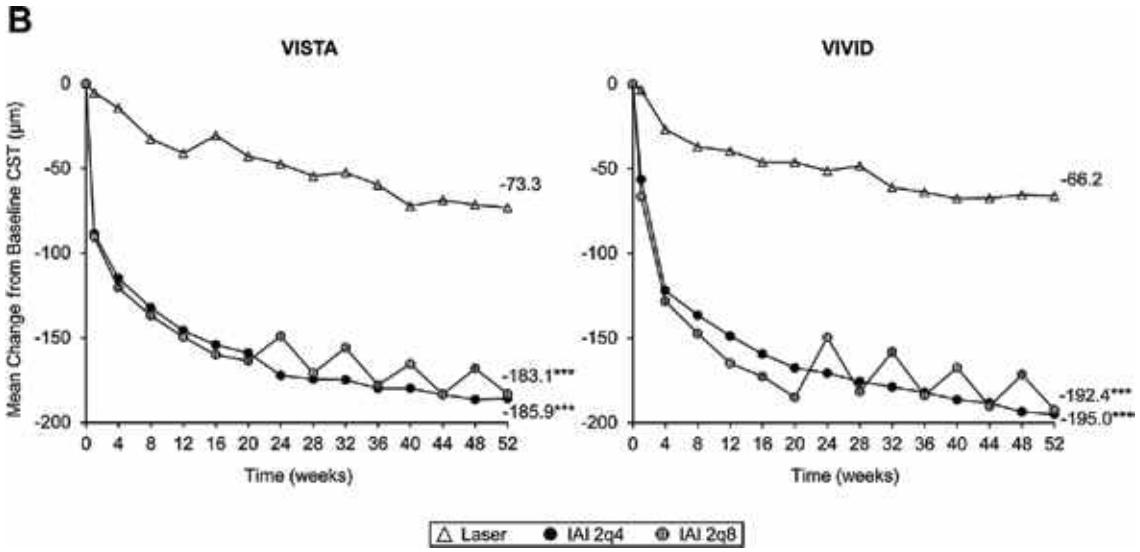


Figure 2: Mean change in central subfield thickness (CST) at week 52.

The study authors note several key differences in these studies compared to other anti-VEGF studies for the treatment of DME3: almost one-fifth of the patients in VIVID were Asian, a substantially higher number than in the RIDE/RISE studies.[3] About 43% of the eyes in VISTA were not treatment-naïve, a subtle (but noteworthy) difference from the RIDE/RISE studies.

Data from these studies led the US FDA to approve Eylea (aflibercept; Regeneron Pharmaceuticals, Inc; Tarrytown, NY) for treatment in patients with DME, with a 2q8 regimen.[8] However, in real-world clinical settings, physicians are questioning if an every-2-month regimen is as beneficial as continual monthly dosing.

Take-Home Points

- Both dosing regimens of IAI (now marketed as Eylea) had significant BCVA improvements at 1 year when compared to laser.
- Improvements in CST, changes in BCVA, and the proportion of patients gaining 15 or more letters were similar between patients who were treatment-naïve and those who had received prior anti-VEGF therapy.

References

1. Boyer DS, Hopkins JJ, Sorof J, Ehrlich JS. Anti-vascular endothelial growth factor therapy for diabetic macular edema. *Ther Adv Endocrinol Metab.* 2013;4(6):151-169.

2. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology.* 2011;118(9):1819-1826.

3. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;21(11):2247-2254.

4. Do DV, Nguyen QD, Boyer D, et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology.* 2012;119(8):1658-1665.

5. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology.* 2011;118(4):615-625.

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(4):789-801.

7. Nguyen QD, Shah SM, Heier JS, et al. Primary end point (six months) results of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology.* 2009;116(11):2175-2181.e1.

8. Eylea [package insert]. Tarrytown, NY: Regeneron; 2014.

VISTA DME

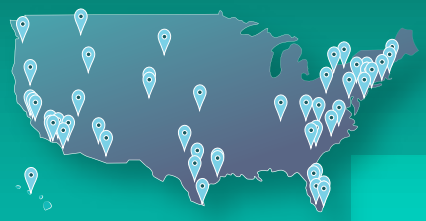
May 2011 - June 2013

A Double-Masked, Randomized, Active-Controlled, Phase III Study of the Efficacy and Safety of Intravitreal Administration of VEGF Trap-Eye in Patients With Diabetic Macular Edema

Phase 3

Sponsor: REGENERON

Collaborator: BAYER



UNITED STATES
54 Sites Nation-wide

TRIAL AGENT

Aflibercept (Intravitreal Aflibercept Injection (IAI)) VS Laser (Macular Laser Therapy (MLT))

STUDY POPULATION

466 eyes, from 466 patients

INCLUSION CRITERIA

- Central Diabetic Macular Edema involvement
- Best-corrected Visual Acuity (BCVA) 24≤ x ≤74 Letters on Early Treatment of Diabetic Retinopathy Study (ETDRS) Chart

TRIAL DESIGN

Double-Blind

- Aflibercept (IAI)
- Sham Injection
- Laser (MLT)
- Sham Laser
- Repeating Regimen

ENDPOINTS (measured at 12 months)

PRIMARY

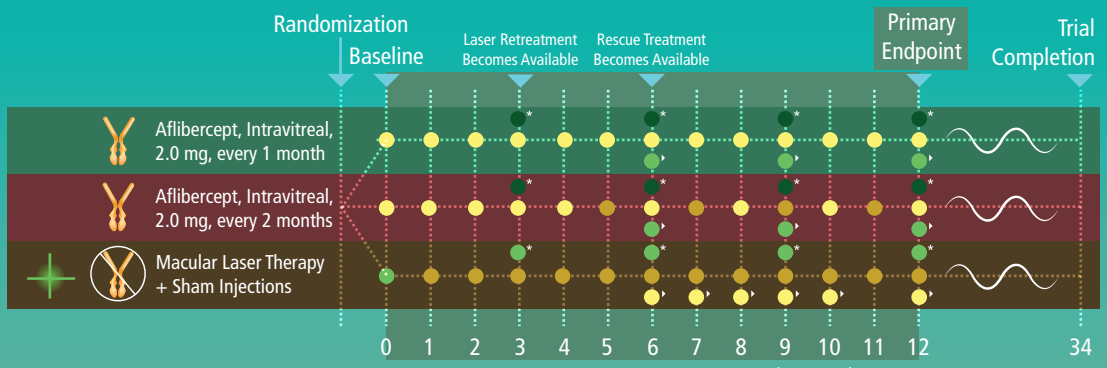
Change in ETDRS Letters

SECONDARY

- % of Eyes that gained ≥10 ETDRS Letters
- % of Eyes that gained ≥15 ETDRS Letters
- % of Eyes that gained ≥2-step improvement in ETDRS Diabetic Retinopathy Severity Scale (DRSS) Score
- Change in Central Subfield Thickness (CST), as measured by Optical Coherance Tomography (OCT)
- Change in National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) near activities subscale score
- Change in NEI VFQ-25 distance activities subscale score

* **Laser Retreatment:** Laser or Sham Laser given (as needed) if thickening of the retina or hard exudates present at ≤ 500 µm of macular center, or ≥1 zone of retinal thickening 1 disc area or larger, any part of which within 1 disc diameter of macula center.

▶ **Rescue Treatment:** Laser given (as needed) if 2q4 and 2q8 patients lost ≥ 10 letters on 2 consecutive visits or ≥ 15 letters at any 1 visit from the best previous measurement, and BCVA was worse than baseline. For MLT patients, 5 doses of IAI 2mg were given every month, followed by a dose every 2 months.

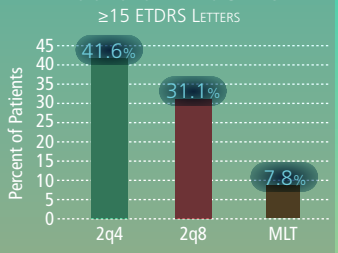


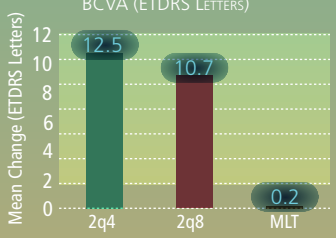
TRIAL ARMS — STUDY TIMELINE (months)

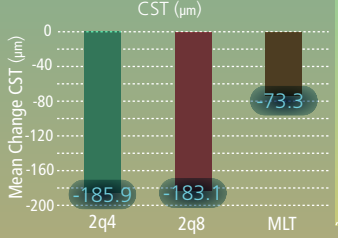
RESULTS

Aflibercept intravitreal injection proved more efficacious in improving vision loss for a greater number of people compared to laser.

- Aflibercept, 2 mg, every 1 month (2q4)
- Aflibercept, 2 mg, every 2 months (2q8)
- Macular Laser Therapy (MLT)





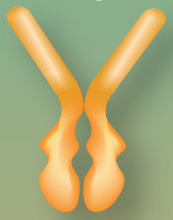


IMPACT

1ST direct comparison between anti-VEGF therapy alone versus laser therapy alone.

- Demonstration of efficacy in non-anti-VEGF naïve eyes
- Based on these results, the FDA approved aflibercept for treatment of DME in July 2014.

SUPERIOR OUTCOMES using



AFLIBERCEPT

* SOURCE - Korobelnik JF, et al. Intravitreal Aflibercept for Diabetic Macular Edema. *Ophthalmology*. 2014 Nov;121(11):2247-54. doi: 10.1016/j.ophtha.2014.05.006. Epub 2014 Jul 8.

VIVID DME

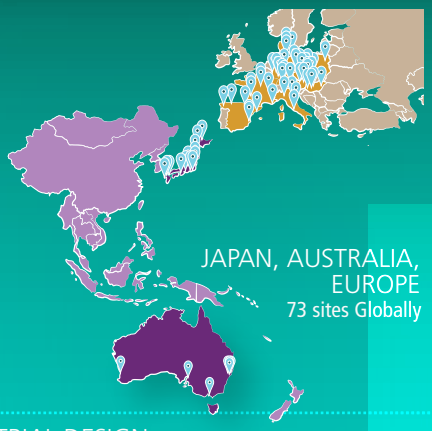
May 2011 - June 2013

A Randomized, Double-Masked, Active Controlled, Phase III Study of the Efficacy and Safety of Repeated Doses of Intravitreal VEGF Trap-Eye in Subjects With Diabetic Macular Edema

Phase 3

REGENERON Sponsor

Collaborator



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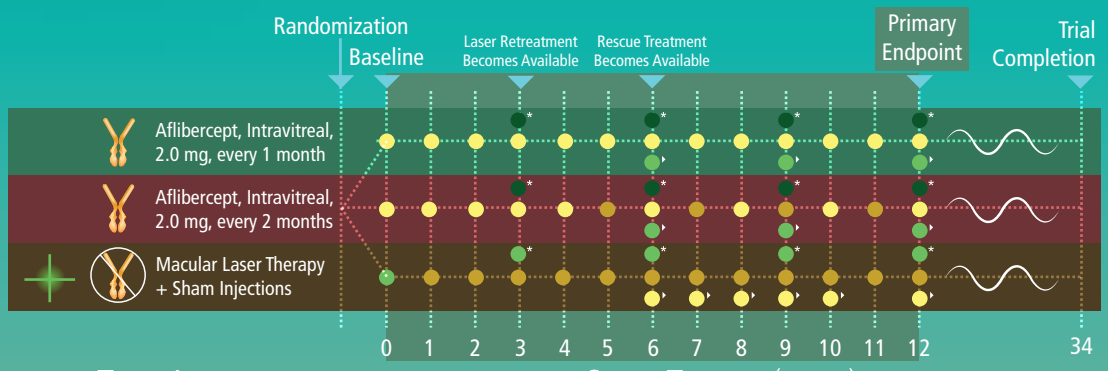

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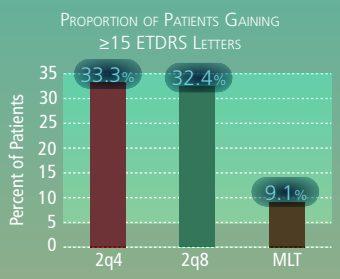

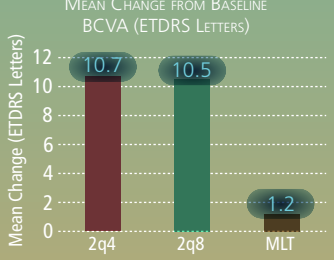

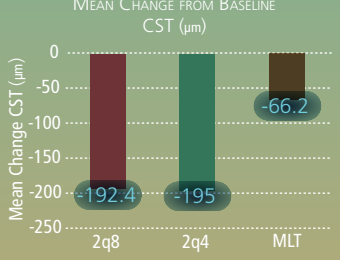

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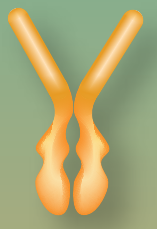

AFLIBERCEPT

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