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Effect of Baseline Subretinal Fluid on Treatment Outcomes in VIVID-DME and VISTA-DME Studies

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Purpose: To evaluate the effect of baseline subretinal fluid (SRF) on treatment outcomes with intravitreal aflibercept injection (IAI) versus laser treatment in patients with diabetic macular edema (DME) in the VIVID and VISTA studies.

Design: Post hoc analysis of 2 randomized controlled trials.

Participants: Eight hundred seventy-two patients with DME.

Methods: We randomized patients to receive IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser.

Main Outcome Measures: Effect of presence or absence of baseline SRF on visual outcomes in the integrated dataset at weeks 52 and 100.

Results: Mean best-corrected visual acuity (BCVA) gains in the 2q4, 2q8, and laser arms at week 52 were +14.5, +11.0, and −2.3 letters, respectively, (those with baseline SRF) and +10.3, +10.6, and +2.5 letters, respectively, (those without). At week 100, mean gains were +13.5, +10.9, and −2.3 letters (those with baseline SRF) and +10.6, +10.0, and +2.7 letters (those without). The treatment effect for IAI versus laser from baseline to week 52 of 100 was greater for patients with baseline SRF versus those without (nominal $P < 0.001$, for interaction). The proportions of patients who gained 15 letters or more in the 2q4, 2q8, and laser arms at week 52 were 52.3%, 40.2%, and 8.9%, respectively, (those with baseline SRF) and 30.9%, 29.1%, and 8.2%, respectively, (those without) and at week 100 were 50.0%, 35.4%, and 12.9%, respectively, (those with baseline SRF) and 33.3%, 30.5%, and 12.5%, respectively, (those without). Time to first sustained SRF clearance seemed to be shorter in the IAI arms versus laser. The overall safety profile was similar in the IAI arms.

Conclusions: This post hoc analysis demonstrated the visual outcome benefits of IAI over laser, regardless of baseline SRF status. A greater treatment effect of IAI was observed in patients with baseline SRF versus those without; however, no meaningful impact of baseline SRF status on treatment outcomes with IAI was demonstrated, indicating that the differential effects of laser might have been the driving force behind the different treatment outcomes in both groups. *Ophthalmology Retina 2019;3:663-669 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

With the increasing prevalence of diabetes worldwide, the ocular complications of this disease, including diabetic macular edema (DME) also have become much more common.[1–6] Current treatment options for DME include macular laser, corticosteroids,[7] and intravitreal injections of anti−vascular endothelial growth factor (VEGF) agents (i.e., aflibercept, ranibizumab, and off-label bevacizumab). Anti−vascular endothelial growth factor agents now are recognized as the treatment of choice in patients with DME compared with previous standards of care.[8–12] Intravitreal aflibercept injections (IAIs) consist of a recombinant fusion protein that currently is indicated for the treatment of neovascular (wet) age-related macular degeneration, macular edema after retinal vein occlusion, myopic choroidal neovascularization, and DME.[13] The VIVID-DME and VISTA-DME studies have shown that IAI is safe and is associated with superior visual and anatomic outcomes compared with laser monotherapy.[14]

Vascular endothelial growth factor induces vascular hyperpermeability and extravasation of blood proteins into the tissues, and subretinal fluid (SRF) is correlated significantly with intraocular VEGF concentrations.[15] The correlation between the presence or absence of baseline SRF and treatment outcomes with anti-VEGF agents has not been studied directly; however, a subanalysis of RISE (A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus) and RIDE (A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus) trials assessing the correlation between baseline SRF and treatment outcomes with ranibizumab in

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patients with DME indicated that the presence of baseline SRF is a good predictor for treatment outcomes, including improvement in visual acuity and resolution of macular edema in patients treated with ranibizumab.[16] Furthermore, a subanalysis of the ranibizumab study READ-3 (Ranibizumab for Edema of the Macula in Diabetes Protocol 3 with High Dose), found that patients with SRF at baseline showed statistically significant greater visual gains than those without baseline SRF.[17] In this post hoc analysis of the VIVID and VISTA studies, we aimed to evaluate the impact of the presence (or absence) of baseline SRF on treatment outcomes with IAI, as well as the treatment effect of IAI versus laser therapy, in patients with DME.

Methods

Study Design

The VIVID (ClinicalTrials.gov identifier, NCT01331681) and VISTA (ClinicalTrials.gov identifier, NCT01363440) study designs and methods have been published previously[14]; key details are summarized here. The VIVID and VISTA studies were 2 similarly designed, phase 3, randomized, double-masked, active-controlled, 148-week trials comparing 2 dosing regimens of IAI with laser control for the treatment of DME. The studies were conducted at 127 sites across Australia, Europe, Japan, and the United States, in accordance with the tenets of the Declaration of Helsinki and with the International Conference on Harmonisation guidelines. Institutional review board or ethics committee approval was obtained at each site before the start of the studies. All patients provided written informed consent.

Adult patients with type 1 or 2 diabetes mellitus who demonstrated DME with central involvement (defined as retinal thickening involving the central 1-mm central subfield thickness) were included if best-corrected visual acuity (BCVA) was between 73 and 24 letters (Snellen equivalent, 20/40−20/320) in the study eye. Only 1 eye per patient was included in the study. Patients were randomized 1:1:1 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. Beginning at week 12, when the laser retreatment criteria were met, study eyes in groups 1 and 2 received sham laser and those in group 3 received active laser, but not more frequently than every 12 weeks. From week 24, additional active treatment (laser in the IAI groups and IAI in the laser control group) was allowed as rescue treatment in cases of disease recurrence or worsening based on prespecified criteria. Patients in the laser control treatment group were eligible to receive IAI treatment in the third year; therefore, we included only data from weeks 52 and 100 in this post hoc analysis.

Outcome Measures

The primary efficacy end point for the VIVID and VISTA studies was the change from baseline BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 52.[14] In our post hoc analysis, we investigated the effect of baseline SRF status (patients with SRF at baseline and patients without SRF at baseline) on treatment outcomes in patients with DME. We integrated data from VIVID and VISTA and examined outcomes at weeks 52 and 100. To determine baseline SRF status, OCT images were evaluated at independent central reading centers (Duke Reading Center, Durham, NC, for VISTA; Vienna Reading Center, Vienna, Austria, for VIVID).

Efficacy end points evaluated in this post hoc analysis include the mean change in BCVA (ETDRS letters) from baseline by baseline SRF status and the treatment effect of IAI versus laser therapy (after adjustment for baseline vision) by baseline SRF status (with vs. without SRF), which was measured by analyzing the BCVA ETDRS letter score. The proportion of patients who gained 15 letters or more in BCVA by baseline SRF status also was evaluated. The corresponding treatment effect of IAI (after adjustment for baseline vision) by baseline SRF status was measured by analyzing the proportion of patients with a 15-letter or more gain from baseline in BCVA. We also assessed the time to first sustained SRF clearance (defined as time to first 2 consecutive readings of no SRF after a reading of SRF at baseline).

Statistical Analysis

Patients included in the full analysis sets (all randomized patients who received any study medication and underwent at least 1 baseline and 1 postbaseline assessment) of the VIVID and VISTA studies were included in the current efficacy analysis. We used an analysis of covariance model to analyze the treatment effect of IAI over laser therapy; baseline visual acuity, treatment, study, baseline SRF status, and the interaction between baseline SRF status and treatment were included as fixed effects. For analysis of the proportion of patients who gained 15 letters or more from baseline at weeks 52 and 100 as stratified by baseline SRF status, we used estimated odds ratios based on a logistic regression model; baseline visual acuity, treatment, study, baseline SRF status, and the interaction between baseline SRF status and treatment were included as fixed effects. For time to first sustained SRF clearance analysis, we used observed cases before dropout or additional treatment, without further imputation for missing values. Patients were censored at the last available visit if no 2 consecutive readings of no SRF after the baseline were observed, whereas those who demonstrated 2 consecutive readings of no SRF after baseline were considered to have an event with time recorded from randomization to the first visit of the 2 consecutive readings of SRF after baseline. With the exception of time to first sustained SRF clearance, missing values were imputed using the last observation carried forward method for all other analyses. For eyes that received additional (rescue) treatment, the last value before additional treatment was carried forward was used. Patients with missing SRF status at baseline were excluded from the SRF subgroup analyses. All analyses with nominal *P* values were performed in an ad hoc fashion without formal multiplicity adjustment. Results may be interpreted as exploratory and hypothesis generating.

Results

In the VIVID and VISTA studies, mean BCVA gains from baseline were greater in the 2q4 and 2q8 arms compared with laser at both week 52 and 100; in addition, a greater proportion of eyes in the IAI groups gained 15 letters or more compared with eyes in the laser control group at both time points.[14]

Post Hoc Analysis

The number of patients demonstrating SRF at baseline in the 2q4, 2q8, and laser arms were 86, 82, and 101, respectively. The corresponding number of patients not demonstrating SRF at baseline were 204, 203, and 184, respectively (Table 1). Mean baseline BCVA was slightly lower in the SRF at baseline group compared with the no SRF at baseline group across all treatment arms (Fig 1; Table 1).

Table 1. Mean Change in Best-Corrected Visual Acuity in Patients with and without Baseline Subretinal Fluid at Weeks 52 and 100*

	Treatment Groups									
	Laser Control		*Intravitreal Aflibercept 2 mg Every 4 Weeks*		*Intravitreal Aflibercept 2 mg Every 8 Weeks*		*Intravitreal Aflibercept 2 mg Every 4 Weeks vs. Laser Therapy,† Least-Squares Mean (Standard Error) Treatment Difference (95% Confidence Interval)*		*Intravitreal Aflibercept 2 mg Every 8 Weeks vs. Laser Therapy,† Least-Squares Mean (Standard Error) Treatment Difference (95% Confidence Interval)*	
With baseline SRF	n = 101		n = 86		n = 82					
Mean baseline BCVA	59.8		57.6		58.2		—		—	
Time points	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100
Mean change in BCVA (SD), ETDRS letters	−2.3 (13.3)	−2.3 (14.5)	14.5 (10.5)	13.5 (15.1)	11.0 (9.3)	10.9 (11.5)	16.45 (13.48–19.41); $P < 0.001$	15.52 (11.91–19.14); $P < 0.001$	13.07 (10.18–15.96); $P < 0.001$	13.02 (9.67–16.38); $P < 0.001$
Without baseline SRF	n = 184		n = 204		n = 203					
Mean baseline BCVA	60.4		60.7		59.5		—		—	
Time points	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100
Mean change in BCVA (SD), ETDRS letters	2.5 (10.1)	2.7 (11.5)	10.3 (8.9)	10.6 (11.3)	10.6 (8.5)	10.0 (10.3)	7.85 (5.78–9.93); $P < 0.001$	7.96 (5.46–10.47); $P < 0.001$	7.96 (5.94–9.99); $P < 0.001$	7.18 (4.84–9.51); $P < 0.001$

— = not available; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; SD = standard deviation; SRF = subretinal fluid.
Patients for whom no baseline assessment of SRF status was available were excluded.
*Integrated data from VIVID and VISTA studies (last observation carried forward, full analysis set).
†The difference in mean change in BCVA in ETDRS letters between the intravitreal aflibercept 2 mg every 4 weeks or 2 mg every 8 weeks groups and the laser therapy group, based on an analysis of covariance model, with baseline visual acuity, treatment, baseline SRF, treatment and baseline SRF interaction, and study as fixed effects.

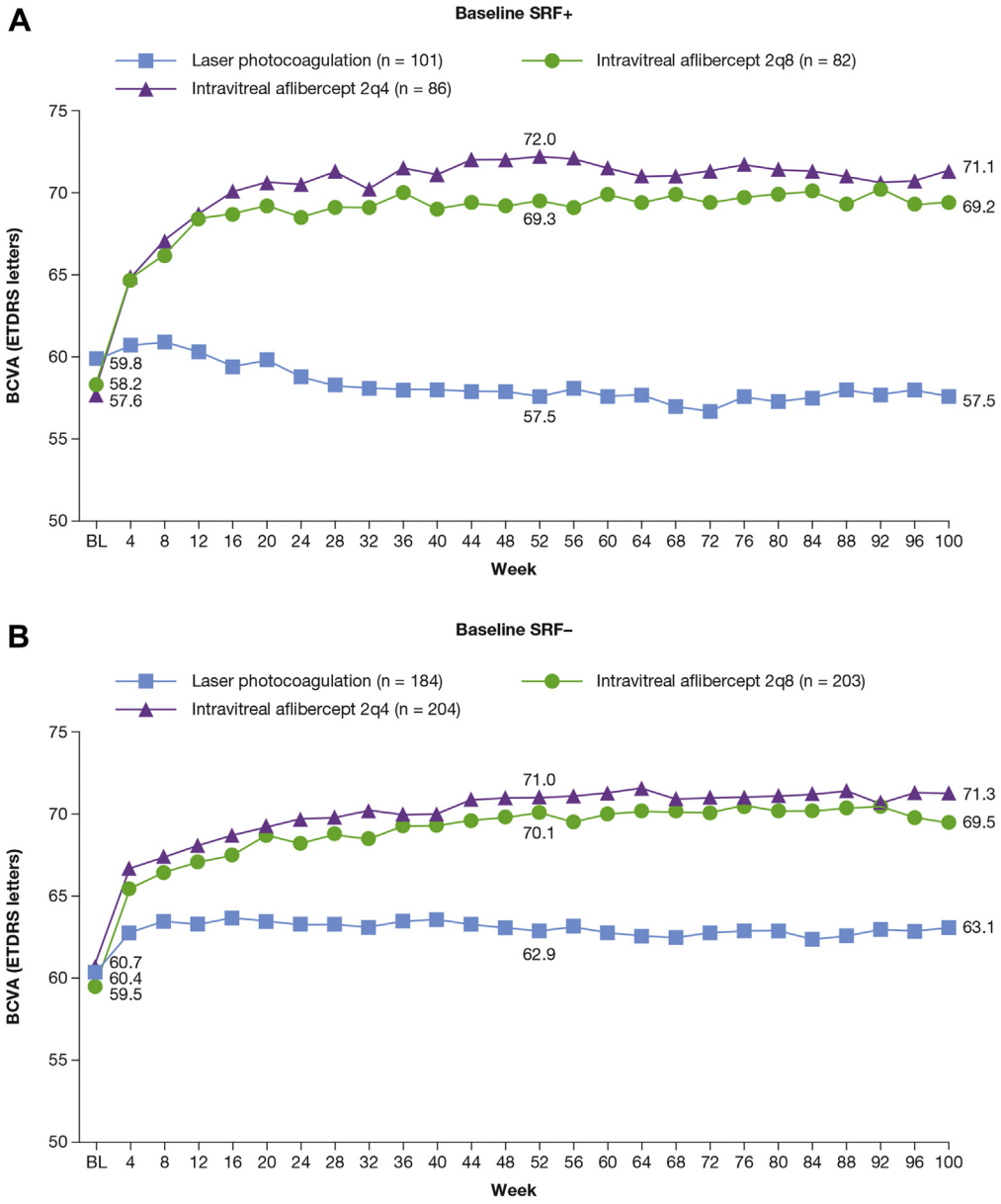

Figure 1. Graphs showing mean change in best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS] letter score) from baseline (BL) to weeks 52 and 100 for patients (**A**) with baseline subretinal fluid and (**B**) without baseline subretinal fluid, last observation carried forward (full analysis set population, VIVID and VISTA combined). Patients who missed SRF status at baseline were excluded. 2q4 = 2-mg intravitreal aflibercept injection every 4 weeks; 2q8 = 2-mg intravitreal aflibercept injection every 8 weeks after receiving 5 initial monthly doses of intravitreal aflibercept.

At week 52, the mean gain in BCVA was greater among patients in the 2q4 and 2q8 arms compared with those in the laser arm, regardless of baseline SRF status (Fig 1; Table 1), which was sustained through week 100 (Fig 1; Table 1). Mean gains in BCVA in the 2q4, 2q8, and laser arms at week 52 were +14.5 letters, +11.0 letters, and −2.3 letters, respectively, for the SRF at baseline group and +10.3 letters, +10.6 letters, and +2.5 letters, respectively, for the no SRF at baseline group. At week 100, mean gains were +13.5 letters, +10.9 letters, and −2.3 letters, respectively, for the SRF at baseline group and +10.6 letters, +10.0 letters, and +2.7 letters, respectively, for the no SRF at baseline group.

The treatment effect for 2q4 and 2q8 versus laser (mean change in ETDRS letter score from baseline to weeks 52 and 100) seemed to be greater for patients with SRF at baseline than for those with no SRF at baseline (Table 1; nominal $P < 0.0001$ for interaction at week 52 for 2q4 and 0.0046 for 2q8; nominal $P < 0.0008$ for interaction at week 100 for 2q4 and 0.0051 for 2q8 [not included in Table 1]) when adjusted for baseline BCVA.

Likewise, a greater proportion of patients in the 2q4 and 2q8 groups gained 15 ETDRS letters or more at weeks 52 and 100 than those treated with laser therapy, regardless of baseline SRF status (Table 2); a numerically greater treatment effect for the IAI groups versus the laser group was observed in the SRF at baseline group

Table 2. Proportion of Patients with or without Baseline Subretinal Fluid Gaining 15 Letters or more in the Study Eye at Weeks 52 and 100*

	Treatment Groups							
	Laser Control		*Intravitreal Aflibercept 2 mg Every 4 Weeks*		*Intravitreal Aflibercept 2 mg Every 8 Weeks*		*Intravitreal Aflibercept 2 mg Every 4 Weeks vs. Laser Therapy,† Estimated Odds Ratio (95% Confidence Interval)*	*Intravitreal Aflibercept 2 mg Every 4 Weeks vs. Laser Therapy,† Estimated Odds Ratio (95% Confidence Interval)*
With baseline SRF	n = 101		n = 86		n = 82			
Time points	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100
Gain ≥15 letters, no. (%)	9 (8.9)	13 (12.9)	45 (52.3)	43 (50.0)	33 (40.2)	29 (35.4)	11.17 (4.96–25.17); $P < 0.0001$	6.64 (3.20–13.76); $P < 0.0001$	6.69 (3.04–15.94); $P < 0.0001$	3.65 (1.73–7.69); $P = 0.0007$
Without baseline SRF	n = 184		n = 204		n = 203			
Time points	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100	Week 52	Week 100
Gain ≥15 letters, no. (%)	15 (8.2)	23 (12.5)	63 (30.9)	68 (33.3)	59 (29.1)	62 (30.5)	5.21 (2.83–9.60); $P < 0.0001$	3.66 (2.15–6.25); $P < 0.0001$	4.68 (2.52–8.71); $P < 0.0001$	3.06 (1.79–5.22); $P < 0.0001$

SRF = subretinal fluid.
Patients for whom no baseline assessment of SRF status was available were excluded.
*Integrated data from VIVID and VISTA studies (last observation carried forward, full analysis set).
†For a gain of ≥15 letters, the odds ratio was calculated to reflect the contrast between the intravitreal aflibercept 2 mg every 4 weeks or 2 mg every 8 weeks groups versus laser, based on a logistic model with baseline visual acuity, treatment, baseline SRF, treatment and baseline SRF interaction, and study in the model.

versus the no SRF at baseline group. The proportion of patients who gained 15 letters or more in the 2q4, 2q8, and laser arms at week 52 was 52.3%, 40.2%, and 8.9%, respectively, for the SRF at baseline group and 30.9%, 29.1%, and 8.2%, respectively, for the no SRF at baseline group. At week 100, the proportion of patients who gained 15 letters or more was 50.0%, 35.4%, and 12.9%, respectively, for the SRF at baseline group and 33.3%, 30.5%, and 12.5%, respectively, for the no SRF at baseline group.

With respect to patients who gained 15 letters or more from baseline at weeks 52 and 100, this ad hoc data indicated no clear significance that baseline SRF affects treatment outcomes in patients receiving 2q4 or 2q8 compared with laser (nominal $P = 0.14$ and $P = 0.45$ for week 52 and $P = 0.19$ and $P = 0.70$ for week 100 for 2q4 and 2q8, respectively). At both time points (weeks 52 and 100), patients with SRF at baseline in the 2q4 and 2q8 arms showed a numerically greater chance of gaining 15 letters or more from baseline than those with no SRF at baseline when compared with the laser therapy group (Table 2).

All but 1 patient with SRF at baseline (98.8%) in the 2q4 arm and all but 3 such patients (96.3%) in the 2q8 arm showed at least 2 consecutive negative SRF readings (i.e., sustained SRF clearance), compared with 80.2% of patients in the laser group who ever experienced sustained SRF clearance (Fig 2).

In the SRF at baseline group, the time to first sustained SRF clearance seemed to be shorter in the 2q4 arm (median, 1.86 months; 95% confidence interval, 0.95−1.87 months) and 2q8 arm (median, 1.12 months; 95% confidence interval, 0.95−1.87 months) compared with the laser arm (median, 4.63 months; 95% confidence interval, 3.71−6.44 months; Fig 2).

The overall incidence of ocular and nonocular serious adverse events was similar across treatment groups in VIVID and VISTA. The most frequent ocular serious adverse event was cataract (3.1%, 2.1%, and 0.3% for the 2q4, 2q8, and laser arms, respectively).[14]

Discussion

In this post hoc analysis, we investigated the impact of baseline SRF status on treatment outcomes in patients enrolled in the VIVID and VISTA studies. Compared with the laser control group, the mean gain in BCVA was greater among patients treated with IAI, regardless of baseline SRF status. Similarly, regardless of baseline SRF status, patients in the IAI groups were more likely to achieve a 15-letter or more gain in BCVA while experiencing shorter times to first sustained SRF clearance than patients treated with laser therapy.

When looking at the change in BCVA at weeks 52 and 100 in patients stratified by baseline SRF status, the treatment effect of IAI over laser therapy was greater in patients with SRF at baseline. This difference in treatment effect at least in part was driven by a greater improvement in BCVA from baseline in laser-treated patients in the no SRF at baseline group compared with the SRF at baseline group (approximately 5-letter difference).

The presence of SRF is considered an indicator of disease activity and is known to have a negative effect on visual function.[16,18] Treatment with anti-VEGF agents reduces retinal fluid volume and improves visual function.[16,19] A post hoc analysis of RISE and RIDE trials of ranibizumab

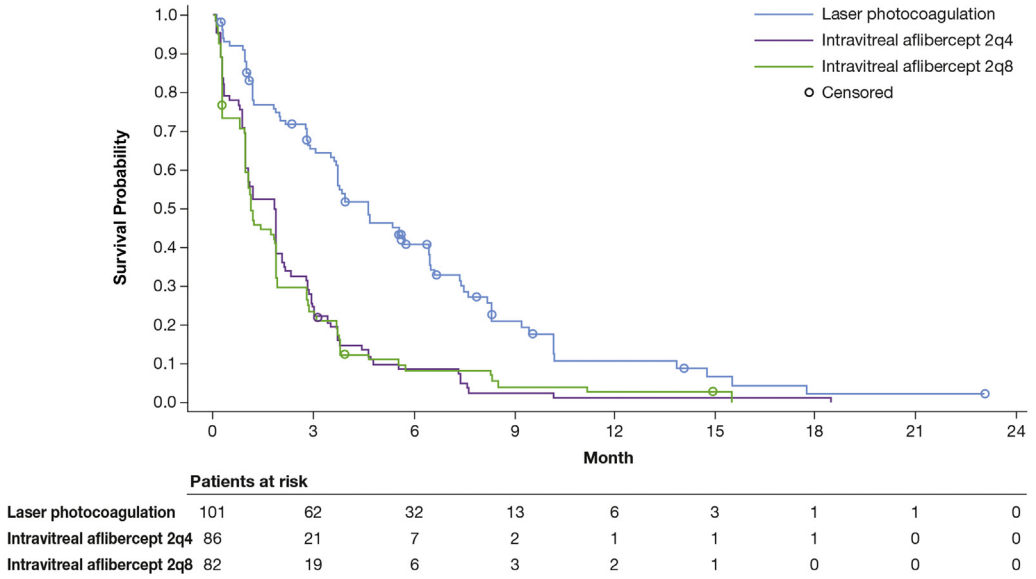

Figure 2. Kaplan-Meier plot showing time to first sustained subretinal fluid (SRF) clearance* for patients with baseline SRF, observed case (full analysis set population, VIVID and VISTA combined). *First sustained SRF clearance is defined as time to first 2 consecutive negative SRF readings after a baseline positive SRF reading. 2q4 = 2-mg intravitreal aflibercept injection every 4 weeks; 2q8 = 2-mg intravitreal aflibercept injection every 8 weeks after receiving 5 initial monthly doses of intravitreal aflibercept.

for the treatment of DME and a retrospective, observational, cohort study of patients with dexamethasone implants indicated that the presence of baseline SRF was predictive for better visual outcomes compared with those without baseline SRF.[16,20] Although our analysis indicates that the gain in BCVA with IAI treatment was similar across the groups with and without SRF at baseline, the treatment effect of IAI versus laser therapy seemed to be greater in the group with SRF at baseline, although mean baseline visual acuity was slightly lower in the SRF at baseline group than in the no SRF at baseline group.

A key limitation of our study is that it was a post hoc analysis rather than a prespecified subgroup analysis. However, the randomized design, fixed dosing, and strict protocols of the VIVID and VISTA studies constitute the strengths of this analysis.

Although the role of SRF as a predictive factor in DME remains to be elucidated fully, this post hoc analysis demonstrated the visual outcome benefits of IAI over laser, regardless of baseline SRF status. Results from the sustained SRF resolution analysis of patients with baseline SRF also supported the anatomic findings, along with the benefits of IAI over laser seen in functional outcomes. Our understanding of the relationship between fluid status and visual acuity outcomes continues to evolve; however, overall, these findings suggest that patients with and without baseline SRF can achieve greater visual gains with IAI treatment compared with laser therapy.

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HUMAN SUBJECTS: Human subjects were included in this study. The studies were conducted in 127 sites in Australia, Europe, Japan, and the United States. Institutional review board or ethics committee approval was obtained at each site before, and informed consent to participate in the study was obtained from all patients. All information presented in this study complies with the Health Insurance Portability and Accountability Act for United States sites. The study was performed in accordance with the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Korobelnik, Lu, Katz, Dhoot, Loewenstein, Arnold, Staurenghi

Analysis and interpretation: Korobelnik, Lu, Katz, Dhoot, Loewenstein, Arnold, Staurenghi

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Abbreviations and Acronyms:
2q4 = intravitreal aflibercept 2 mg every 4 weeks; **2q8** = intravitreal aflibercept 2 mg every 8 weeks following 5 initial monthly doses; **BCVA** = best-corrected visual acuity; **DME** = diabetic macular edema; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FAS** = full analysis set; **IAI** = intravitreal aflibercept injection; **LOCF** = last observation carried forward; **OC** = observed case; **READ-3** = Ranibizumab for Edema of the macula in Diabetes-Protocol 3 with High Dose; **RIDE** = A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus; **RISE** = A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus; **SRF** = subretinal fluid; **VEGF** = vascular endothelial growth factor.

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