ORIGINAL ARTICLE

Efficacy and Safety of Intravitreal Aflibercept Treat-and-Extend for Macular Edema in Central Retinal Vein Occlusion: the CENTERA Study

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• PURPOSE: To evaluate the efficacy and safety of intravitreal aflibercept (IVT-AFL) treat-and-extend dosing in patients with macular edema secondary to central retinal vein occlusion (CRVO).

• DESIGN: CENTERA (Evaluation of a Treat and Extend Regimen of Intravitreal Aflibercept for Macular Edema Secondary to CRVO; NCT02800642) was an open-label, Phase 4 clinical study.

• METHODS: Patients received 2 mg of IVT-AFL at baseline and every 4 weeks thereafter, until disease stability criteria were met (or until week 20), at which point treatment intervals were adjusted in 2-week increments based on functional and anatomic outcomes.

• RESULTS: From baseline to week 76, 105 patients (65.6%) (P <.0001 [test against threshold of 40%]) gained ≥15 letters; and, during the treat-and-extend phase, 72 patients (45.0%) (P = 0.8822 [test against threshold of 50%]) achieved a mean treatment interval of ≥8 weeks. A last and next planned treatment interval of ≥8 weeks was achieved by 101 patients (63.1%) and by 108 patients (67.5%), respectively. Mean ± SD best-corrected visual acuity increased from 51.9 ± 16.8 letters at baseline to 72.3 ± 18.5 letters at week 76 (mean change: +20.3 ± 19.5 letters), and central retinal thickness decreased from 759.9 ± 246.0 μm at baseline to 265.4 ± 57.9 μm at week 76 (mean change: −496.1 ± 252.4 μm). The safety profile of IVT-AFL was consistent with that of previous studies.

• CONCLUSIONS: Clinically meaningful improvements in functional and anatomic outcomes were achieved with IVT-AFL treat-and-extend dosing. Most patients achieved a last actual and last intended treatment interval of ≥8 weeks; therefore, treatment intervals may have been extended even further with a longer study duration. (Am J Ophthalmol 2021;227: 106–115.

Retinal vein occlusion is a common cause of vision loss in patients with chronic macular edema.[1] There are 3 different types of retinal vein occlusions, based on the obstruction site: branch retinal vein occlusion, central retinal vein occlusion (CRVO), and hemiretinal vein occlusion.[2] CRVO is an obstruction of the main retinal vein at or posterior to the optic nerve head[3]; it affects both men and women and occurs most commonly in patients who are 60 years of age or older.[2, 4] Although CRVO is usually unilateral,[4] approximately 7.8% of patients with CRVO in one eye also have RVO in the fellow eye.[5] CRVO leads to impaired venous drainage from the eye, which in turn may result in increased venous pressure, reduced arterial perfusion, and retinal ischemia. Retinal nonperfusion leads to an increase in vascular endothelial growth factor (VEGF), which increases vascular permeability and can cause macular edema, retinal hemorrhage, and neovascularization.[6]

Treatment of macular edema secondary to CRVO involves the administration of anti-VEGF agents, such as aflibercept and ranibizumab, which have become the standard of care. The efficacy and safety of intravitreal aflibercept (IVT-AFL) were assessed in 2 pivotal Phase 3 studies, COPERNICUS (NCT00943072)[7, 8] and GALILEO (Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion; NCT01012973),[9, 10] in which findings demon-

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strated that IVT-AFL was beneficial for the treatment of macular edema secondary to CRVO. In these studies, the mean change from baseline to week 24 in best-corrected visual acuity (BCVA) was +17.3 and +18.0 letters for patients treated with IVT-AFL compared with −4.0 and +3.3 letters in patients who received sham injections, respectively.[7, 10] These studies demonstrate how, if left untreated, patients with macular edema secondary to CRVO lose VA and have a poor prognosis. This was similarly shown in the CRUISE study (A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion; NCT00485836), in which mean change from baseline BCVA at month 6 was +12.7 letters and +14.9 letters in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, and +0.8 letters in the sham group.[11] Both the COPERNICUS and the GALILEO studies included *pro re nata* (PRN) dosing from week 24 of treatment to investigate the possibility of extending the treatment interval beyond 4 weeks. Post hoc assessment of the different dosing subgroups demonstrated some de-stabilization of the disease with doses administered PRN. Although the deterioration seen during the study period was minor, possibly due to the regular monitoring schedule implemented in those trials, it is likely to progress over the expected longer-term treatment duration required in the real-world setting for patients with macular edema secondary to CRVO.

The Lucentis, Eylea, Avastin in Vein Occlusion (LEAVO) study (ISRCTN13623634) compared IVT-AFL, bevacizumab, and ranibizumab using a PRN dosing regimen and introduced a threshold of treatment success for suspending treatment (>83 Early Treatment Diabetic Retinopathy Study [ETDRS] letters), which allowed a comparative assessment of the treatment burden associated with each treatment arm.[12] Treatment with any of these 3 anti-VEGF agents resulted in improved and sustained VA when patients were monitored regularly and treated promptly (IVT-AFL: +15.1 letters; ranibizumab: +12.5 letters; and bevacizumab: +9.8 letters at week 100). Notably, IVT-AFL was non-inferior to ranibizumab at week 100.

Post hoc analyses of COPERNICUS and GALILEO supported the implementation of proactive treatment to prevent deterioration of functional and anatomic outcomes. "Treat and extend" is a proactive, individualized dose strategy whereby the patient receives an injection at every visit. The treatment interval is decided at every visit and is gradually extended if functional and anatomic stability are maintained and shortened if deterioration is observed, to minimize the risk of disease recurrence rather than in response to it.[13] Additionally, with treat-and-extend dosing regimens, the need for interim monitoring is minimized, which reduces the number of appointments per patient and minimizes the need for monitoring visits.[14] Decreasing the number of visits per patient reduces the treatment burden and the need for scheduling visits, thus benefiting both the patient and the health care providers.

To our knowledge, treat-and-extend dosing regimens have not been evaluated in large-scale studies of IVT-AFL for the treatment of macular edema secondary to CRVO. Therefore, the aim of the CENTERA (Evaluation of a Treat and Extend Regimen of Intravitreal Aflibercept for Macular Edema Secondary to CRVO; NCT02800642) study was to assess the efficacy and safety of IVT-AFL administered in a treat-and-extend dosing regimen in patients with macular edema secondary to CRVO.

METHODS

• **STUDY DESIGN:** CENTERA (NCT02800642) was a 76-week, multicenter, open-label, single-arm, Phase 4 study that assessed the efficacy and safety of IVT-AFL administered using a treat-and-extend dosing regimen in treatment-naive patients with macular edema secondary to CRVO. CENTERA was conducted between June 2016 and July 2019 at 42 study centers in Australia, Canada, Denmark, France, Germany, Italy, Spain, and the UK, in accordance with the Declaration of Helsinki and the International Council for Harmonisation guideline E6: Good Clinical Practice. The protocol and any amendments were reviewed and approved by each study site's Independent Ethics Committee or Institutional Review Board (IRB) before the start of the study. The name of each study site's IRB is listed in Supplemental Table 1. All enrolled patients provided written informed consent.

• **PARTICIPANTS:** Treatment-naive patients ≥18 years of age with center-involved macular edema secondary to CRVO for no longer than 3 months were enrolled. Patients were required to have a BCVA of 73-24 ETDRS letters (Snellen equivalent of 20/40-20/320) in the study eye. All patients were scheduled to be treated with IVT-AFL as part of routine clinical practice, with the intent to use a treat-and-extend regimen after the initial dose. Exclusion criteria are listed in the Supplemental material.

• **INTERVENTIONS:** CENTERA was a single-arm study, and patients received treatment at the discretion of the physician. All patients received 2-mg IVT-AFL injections at baseline and every 4 weeks until disease stability criteria were met or until week 20, whichever occurred first (the initiation phase of the treatment). Starting at week 8, the re-treatment interval was determined, and the frequency of injections could be adjusted by 2-week increments to maintain stable functional and anatomic outcomes (the treat-and-extend phase of treatment).

The stability criteria were no new cysts found on optical coherence tomography; BCVA within a ±5-letter "stability corridor" (defined as no more than a 5-letter gain as the last or second to last visit and no more than a 5-letter loss from

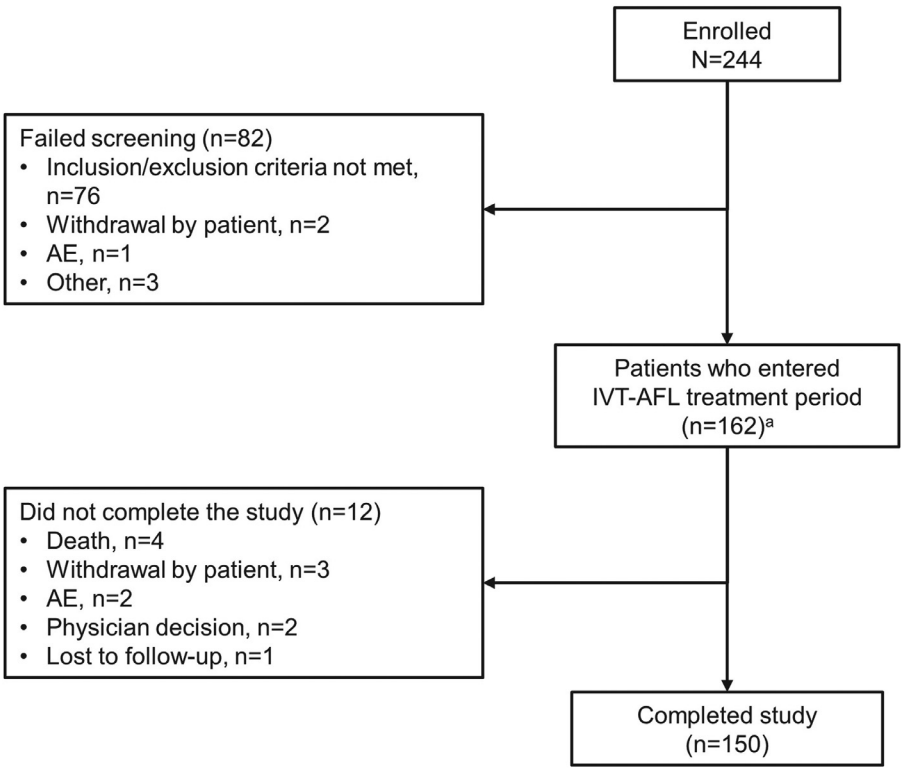

FIGURE 1. Patient disposition. Two patients had no post-baseline assessments available and were not included in the full analysis set. AE = adverse event; IVT-AFL = intravitreal aflibercept.

best previous BCVA at any visit); and central retinal thickness (CRT) within a ±20% "stability corridor" (defined as no more than 20% thickness reduction as the last or second to last visit and no more than 20% thickening from best previous CRT at any visit). Values of BCVA and CRT outside those "stability corridors" were considered "improvements" for higher BCVA values and lower CRT values and "deteriorations" for lower BCVA values and higher CRT values.

From week 8, at every treatment visit (and at weeks 24, 52, and 76), the physician determined the stability status of each patient, and the following algorithm was used to determine the re-treatment interval: if the condition was stable (all stability criteria met), the treatment interval was extended by 2 weeks. If the condition was improving (no new cysts and improvement in at least 1 of the disease activity criteria [BCVA or CRT] with the other improving or stable), the treatment interval was maintained; and if the condition was deteriorating (new cysts and/or deterioration in at least 1 of the other disease activity criteria [BCVA or CRT]), the treatment interval was reduced by 2 weeks. Injections were not to be administered more frequently than every 4 weeks (minimum re-treatment interval).

• **STUDY ENDPOINTS:** The pre-determined co-primary endpoints were the proportion of patients who gained ≥15 letters from baseline to week 76 and the proportion of patients with a mean treatment interval of ≥8 weeks from the last initiation phase visit to week 76. These endpoints were met if significantly ≥40% of patients gained ≥15 letters and if significantly ≥50% of patients had a mean treatment interval of ≥8 weeks.

Secondary endpoints included mean change in BCVA and CRT from baseline to weeks 24, 52, and 76; the number of injections from baseline to week 76; and the mean treatment interval from baseline to week 76. Other endpoints reported included the proportion of patients who lost <15 letters. The following post hoc analyses were also conducted: the proportion of patients who achieved a last actual (defined as the length of the interval before study end [last]) and last intended treatment interval (defined as the next planned interval [next planned]) of ≥8 weeks and the proportion of patients who had a BCVA of ≥70 letters at all mandatory study visits. Safety was assessed throughout the study period. Adverse events (AEs) were treatment-emergent if they occurred or worsened after the first IVT-AFL dose and, at most, 30 days after the last dose. All AEs were reported in case report forms and coded using Medical Dictionary for Regulatory Activities, edition 22.0. An adjudication of AEs according to the Antiplatelet Trialists' Collaboration criteria was also performed.

• **STATISTICAL ANALYSIS:** Study success required that a gain of ≥15 letters at week 76 was reached by significantly more than 40% of patients and that a mean treatment interval of ≥8 weeks was reached by significantly more than 50% of patients during the treat-and-extend phase. The ex-

act 1-sample binomial test was used to assess each of the co-primary efficacy variables at a significance level of 5% (2-sided test) using the full analysis set (FAS), and 95% confidence intervals (CIs) were provided. A sample size of 150 patients was calculated to provide a power of ≥90% to meet both co-primary endpoints, assuming a true probability for gaining ≥15 letters of 55% and a true probability to reach a mean treatment interval of ≥8 weeks of 65%. All other variables were analyzed by descriptive statistical methods, and frequency tables were generated for categorical data.

The safety analysis set included all enrolled patients who received IVT-AFL. The FAS included all enrolled patients who received IVT-AFL, had a baseline BCVA assessment, and had at least 1 post-baseline BCVA assessment. The primary efficacy analysis was conducted using the FAS. The per-protocol set (PPS) included all enrolled patients who received IVT-AFL, had a BCVA assessment at study baseline, had at least 1 BCVA assessment at week 24 or later, and did not have a major protocol deviation. The co-primary efficacy variable sensitivity analysis was conducted using the PPS. Statistical evaluation was performed using Statistical Analysis System version 9.4 software (SAS Institute, Cary, North Carolina, USA).

RESULTS

• **PATIENTS:** Of the 244 patients who were enrolled, 162 completed screening and entered the treatment period. Two patients had no post-baseline assessments available and were not included in the FAS. Overall, 150 patients (92.6%) completed the study. The reasons for study discontinuation were death (n = 4), withdrawal by patient (n = 3), AEs (n = 2), physician decision (n = 2), and lost to follow-up (n = 1). In total, 147 patients were included in the PPS (Figure 1).

The overall mean ± SD age was 66.2 ± 13.4 years, and 60.0% of patients were male (Table 1). At baseline, mean ± SD BCVA was 51.9 ± 16.9 letters and CRT was 759.9 ± 246.0 µm.

• **TREATMENT EXPOSURE:** Patients received a mean 5.3 ± 0.7 (baseline to week 24), 3.9 ± 1.3 (weeks 24-52), and 3.0 ± 1.3 (weeks 52-76) IVT-AFL injections. Of those who completed treatment (n = 150), the mean treatment interval in the treat-and-extend phase was 7.6 ± 1.9 weeks, and the mean length of the last and next planned treatment intervals were 9.3 ± 3.5 weeks and 9.7 ± 3.8 weeks, respectively. Overall, 25.6% (n = 41) and 36.9% (n = 59) of patients achieved a last and a next planned treatment interval of ≥12 weeks, respectively.

• **EFFICACY:** In total, 105 patients (65.6%; 95% CI, 57.7-72.9; $P < .0001$ [test against threshold of 40%]) gained ≥15 letters from baseline to week 76. Overall, 72 patients (45.0%; 95% CI, 37.1-53.1; $P = .8822$ [test against threshold of 50%]) achieved a mean treatment interval of ≥8 weeks during the treat-and-extend phase. Additionally, 101 patients (63.1%) achieved a last and 108 patients (67.5%) achieved a next planned treatment interval of ≥8 weeks.

A sensitivity analysis of the coprimary efficacy variables conducted using the PPS provided results similar to the primary analysis of the FAS: 98 patients (66.7%; 95% CI, 58.4-74.2) gained ≥15 letters from baseline to week 76 and 70 patients (47.6%; 95% CI, 39.3–56.0) achieved a mean treatment interval of ≥8 weeks during the treat-and-extend phase.

Clinically meaningful improvements in mean BCVA were observed at all mandatory visits. Mean ± SD BCVA was 51.9 ± 16.8 letters at baseline and 72.3 ± 18.5 letters at week 76 (mean change: +20.3 ± 19.5 letters) (Figure 2).

Overall, 112 patients (70.0% gained ≥15 letters, and 153 patients (95.6%) maintained vision (<15 letters loss) from baseline to week 76 in the FAS (last observation carried forward). Categorical BCVA gains and losses from baseline to week 76 are shown in Supplemental Figure 1.

In a post hoc analysis of the FAS, 22 patients (13.8%) had a baseline BCVA of ≥70 letters (20/40 Snellen equivalent), which increased to 107 patients (66.9%) at week 76 (last observation carried forward). Overall, 96 patients (60.0%) included in the FAS had a BCVA of ≥70 letters at all mandatory study visits (weeks 24, 52, and 76).

Clinically meaningful improvements in mean CRT were observed at all mandatory visits. Mean ± SD CRT decreased from 759.9 ± 246.0 µm at baseline to 265.4 ± 57.9 µm at week 76 (mean change: −496.1 ± 252.4 µm) (Figure 3).

• **SAFETY:** In total, 131 patients (80.9%) reported at least 2 treatment-emergent AEs (TEAEs) during the study, and these TEAEs were predominantly mild or moderate in severity (Table 2). Overall, 90 patients (55.6%) reported ocular TEAEs in the study eye, the most common of which were reduced VA (24 patients; 14.8%), increased intraocular pressure (20 patients; 12.3%), conjunctival hemorrhage (15 patients; 9.3%), and retinal ischemia (15 patients; 9.3%). No cases of endophthalmitis were reported. A listing of ocular TEAEs ≥1% in the study eye is reported in Supplemental Table 2.

Serious TEAEs were reported in 32 patients (19.8%), and 8 patients (4.9%) experienced serious ocular TEAEs in the study eye. One case of intraocular inflammation, iridocyclitis, and 1 case of retinal artery occlusion (0.6% each) were assessed as serious TEAEs related to IVT-AFL. In total, there were 4 deaths reported; one patient had an Antiplatelet Trialists' Collaboration event (pulmonary embolism; the patient also experienced a lower respiratory tract infection and atrial flutter). The other 3 deaths reportedly were due to B-cell lymphoma, intestinal perforation, and pneumonia (n = 1 each). Two deaths were treatment-emergent, and none were assessed as being related to IVT-AFL.

TABLE 1. Patient Baseline Demographics and Disease Characteristics

Characteristic	IVT-AFLN=160
Mean age, years (SD)	66.2 (13.4)
Age range, years, n (%)	
18–64	62 (38.8)
65–84	87 (54.4)
≥85	11 (6.9)
Sex, n (%)	
Male	96 (60.0)
Race, n (%)	
White	152 (95.0)
Asian	3 (1.9)
Black	1 (0.6)
Not reported	4 (2.5)
Mean BVCA ETDRS letters, (SD)	51.9 (16.9)
Mean CRT, μm (SD)[a]	759.9 (246.0)
Weeks since CRVO diagnosis, n (%)[b]	
0	3 (1.9)
1	35 (22.3)
2	43 (27.4)
3	21 (13.4)
4	13 (8.3)
5	8 (5.1)
6	9 (5.7)
7	5 (3.2)
8	3 (1.9)
9	3 (1.9)
≥10	17 (10.8)
Mean refraction sphere, diopters (SD)	1.8 (1.7)
Capillary non-perfusion on FA, n (%)	
No	149 (93.1)
Yes	11 (6.9)
Location of capillary non-perfusion on FA, n (%)	
Q1, Q2, Q3, Q4	6 (3.8)
Q2, Q3	3 (1.9)
Q3	2 (1.3)
Gonioscopy, n (%)	
Normal	148 (92.5)
Abnormal	9 (5.6)
Missing	3 (1.9)

[a] n=158

[b] n=157.

Full analysis set. BVCA = best-corrected visual acuity; CRT = central retinal thickness; CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; IVT-AF = intravitreal aflibercept; Q = quadrant; SD = standard deviation.

DISCUSSION

CENTERA was among the first studies to evaluate IVT-AFL administered in a treat-and-extend dosing regimen for the treatment of macular edema secondary to CRVO on a relatively large scale.

This study showed that IVT-AFL administered in a treat-and-extend dosing regimen improved functional and anatomic outcomes in patients with macular edema secondary to CRVO over 76 weeks. Overall, 66% of patients gained ≥15 letters from baseline to week 76; conversely, the proportion of patients who achieved a mean treatment interval of ≥8 weeks between the last initiation phase visit

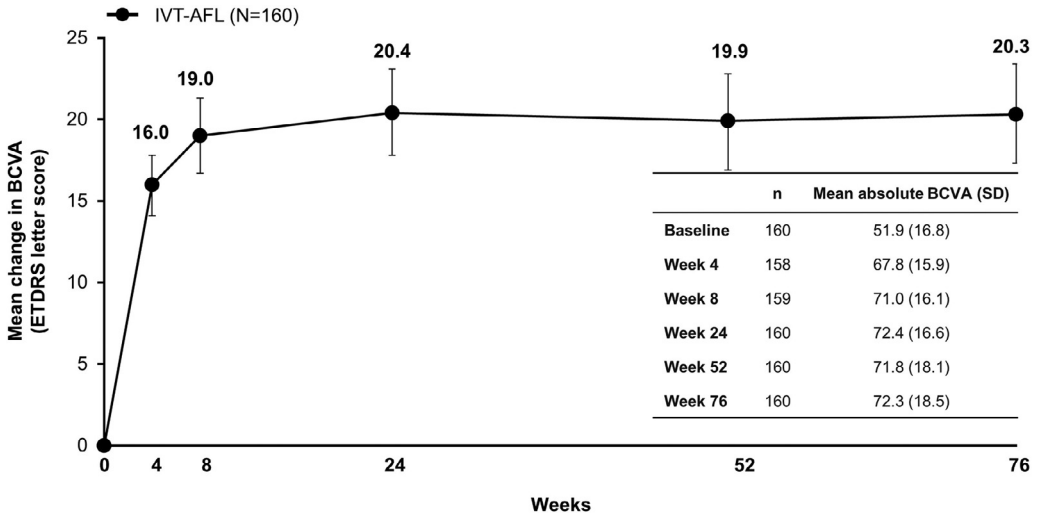

FIGURE 2. Mean change in BCVA from baseline to week 76. Full analysis set; last observation carried forward. Error bars are 95% confidence intervals. BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT-AF = intravitreal aflibercept; SD = standard deviation.

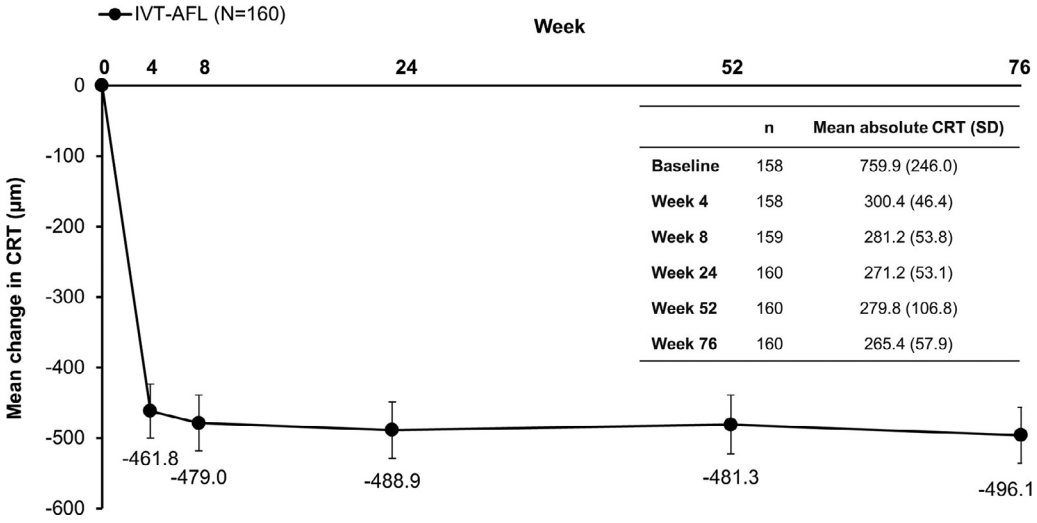

FIGURE 3. Mean change in CRT from baseline to week 76. Full analysis set; last observation carried forward. Error bars are 95% confidence intervals. Change at week 4, n = 156; n = 157 at week 8; and n = 158 at weeks 24, 52, and 72. CRT = central retinal thickness; IVT-AFL = intravitreal aflibercept; SD = standard deviation.

and week 76 did not reach statistical significance. The robustness of these results was further demonstrated in a sensitivity analysis of the PPS.

Although fewer than half of patients achieved a mean treatment interval of ≥8 weeks, post hoc analysis demonstrated that 63% and 68% of patients achieved a last and next planned treatment interval of ≥8 weeks, respectively. Functional and anatomic improvements were achieved with a mean of 5 injections (baseline to week 24), 4 injections (weeks 24-52), and 3 injections (weeks 52-76). As expected with the treat-and-extend treatment paradigm, treatment burden was highest during the initiation phase and decreased over time. The downward trend in the intensity of the treatment pattern through to the end of the study further supports the notion that a mean treatment interval of ≥8 weeks between the last initiation phase visit and week 76 might have been met with the implementation of a longer observation period.

Clinically meaningful improvements in BCVA were observed at all mandatory study visits, with a mean change

TABLE 2. Safety Overview at Week 76

Number of patients (%)	IVT-AFL N=162
Any AE	134 (82.7)
Any ocular AE	103 (63.6)
Any TEAE	131 (80.9)
Any ocular TEAE	98 (60.5)
Any ocular TEAE in the study eye	90 (55.6)
Any ocular TEAE in the fellow eye	56 (34.6)
Any non-ocular TEAE	106 (65.4)
Any TEAE related to study drug	6 (3.7)
Any TEAE related to IVT injection procedure	48 (29.6)
Any TEAE related to other procedures required by the protocol	10 (6.2)
Maximum intensity for any TEAE	
Mild	41 (25.3)
Moderate	70 (43.2)
Severe	20 (12.3)
Ocular TEAEs in the study eye ≥5%	
Visual acuity reduced	24 (14.8)
Increased intraocular pressure	20 (12.3)
Conjunctival hemorrhage	15 (9.3)
Retinal ischemia	15 (9.3)
Macular edema	10 (6.2)
Foreign body sensation	9 (5.6)
Retinal hemorrhage	9 (5.6)
Vitreous detachment	9 (5.6)
Any SAE	37 (22.8)
Any treatment-emergent SAE	32 (19.8)
Any treatment-emergent SAE related to study drug[a]	2 (1.2)
Any treatment-emergent SAE related to IVT injection[a] procedure	2 (1.2)
Any treatment-emergent SAE causally related to other procedures required by the protocol	0
Discontinuation of study drug due to AEs	6 (3.7)
Discontinuation of study drug due to TEAEs	2 (1.2)
Any APTC event	1 (0.6)
Any deaths	4 (2.5)
Any treatment-emergent deaths	2 (1.2)

[a]Both cases were related to study drug and IVT injection procedure.

Safety analysis set. AE = adverse event; APTC = Anti-Platelet Trialists' Collaboration; IVT = intravitreal; IVT-AFL = intravitreal aflibercept; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

from baseline of +20 letters at week 76. Results of a post hoc analysis showed that, by week 76, 67% of patients had a BCVA of ≥70 letters, which is a threshold for maintaining a driving license in many countries. Clinically meaningful improvements in anatomic outcomes were also observed at all mandatory study visits, with a mean change in CRT of −496 μm at week 76. Most of the reduction in CRT was seen following the first IVT-AFL injection (−462 μm at week 4). It is also worth noting that 73% of patients were treated within 4 weeks of diagnosis. The safety profile of IVT-AFL was consistent with that in previous studies.[8, 9] Notably, there were no cases of endophthalmitis and only 1 case of intraocular inflammation.

The functional and anatomic outcomes achieved in CENTERA using a treat-and-extend regimen are similar to those seen in other studies of IVT-AFL with monthly or PRN dosing.[8, 9, 12, 15] The mean change in BCVA from baseline to week 24 was +20 letters in CENTERA, +17 letters in COPERNICUS,[7] +18 letters in GALILEO,[10] +19 letters in SCORE-2: Study of COmparative Treatments for REtinal Vein Occlusion 2,[15] and +13 letters in LEAVO.[12] The mean change in CRT from baseline to week 52 was −481 μm in CENTERA, −413 μm in COPERNICUS, and −424 μm GALILEO[8, 9].

Most patients in the CENTERA study had nonischemic CRVO (93%). In the COPERNICUS[7] and VIBRANT: Study to Assess the Clinical Efficacy and Safety of Intravit-

real Aflibercept Injection (IAI;EYLEA®;BAY86-5321) in Patients With Branch Retinal Vein Occlusion[16] studies of IVT-AFL, a smaller proportion of patients had nonischemic disease, 67.5% and 60.4%, respectively. In all 3 studies, patients showed improvements in functional and anatomic outcomes, therefore indicating that IVT-AFL therapy was effective in patients with both ischemic and nonischemic CRVO.

The importance of differentiating fluid compartments is gaining increasing attention in neovascular age-related macular degeneration (nAMD), whereby fluid compartments have been shown to have differential effects on functional outcomes.[17] It is feasible that tolerance of anti-VEGF-resistant fluid in specific compartments (such as subretinal fluid) may allow extension of intervals while maintaining good functional outcomes. However, the impact of such an approach on the treatment of macular edema secondary to CRVO has yet to be explored. Additionally, possibly more so than in nAMD, the treatment burden in CRVO significantly lessens over time as the disease appears to stablize more effectively, potentially enabling further extension of treatment intervals as the disease stabilizes.

Further data, including those from the LEAVO study, suggest that a lower treatment intensity may have a detrimental impact on functional outcomes. It is possible that the lower number of injections through 52 weeks in LEAVO compared with those in CENTERA (approximately 7.0 vs. 9.2 injections, respectively) allowed for persistent fluid and more recurrence. Initial monthly dosages for CRVO may need to be more protracted than the typical treatment schedule of 3 initial monthly doses in nAMD.

Published studies, including LEAVO,[12] have also demonstrated the superior durability of IVT-AFL compared with ranibizumab, as shown by the lower mean number of injections over 100 weeks with IVT-AFL (10.0 vs. 11.8 injections, respectively). However, the vision gains in LEAVO at 100 weeks (+15 letters for IVT-AFL) were not as high as those reported in CENTERA at 76 weeks (+20 letters), possibly supporting the requirement for proactive treatment (such as treat-and-extend) in patients with CRVO.

This study had a number of strengths, including a high statistical power of ≥90%, inclusion of a broad range of baseline visual function (73-24 ETDRS letters; 20/40-20/320 Snellen equivalent) and early initiation of treatment. Limitations of this study are that it was a single-arm study with no active comparator, thus potentially limiting interpretation of the results. However, the single-arm design was chosen to evaluate the utility of the treat-and-extend regimen in patients with CRVO, as this regimen has not previously been analyzed in large clinical studies within this patient population. Furthermore, analysis of the last and next planned treatment intervals was post hoc in nature, which limited interpretation of the data.

Overall, clinically meaningful and significant improvements in functional and anatomic outcomes were achieved with IVT-AFL administered using a treat-and-extend regimen in patients with macular edema secondary to CRVO. Treatment intervals were also extended, and most patients achieved a last and next planned treatment interval of ≥8 weeks.

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

TOC

CENTERA (Evaluation of a Treat and Extend Regimen of Intravitreal Aflibercept for Macular Edema Secondary to CRVO; NCT02800642) evaluated the efficacy and safety of intravitreal aflibercept treat-and-extend dosing in patients with macular edema secondary to central retinal vein occlusion. Overall, clinically meaningful improvements in functional and anatomic outcomes were achieved. Treatment intervals were extended, and most of the patients achieved last and next planned treatment intervals of ≥8 weeks. These results support the use of intravitreal aflibercept treat-and-extend dosing in patients with macular edema in central retinal vein occlusion within clinical practice.

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As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014.

Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal.

Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajo.2021.01.027.

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