

# Ophthalmology Times<sup>®</sup>

**SUPPLEMENT**

*EUROPE*

## **Efficacy and safety of intravitreal aflibercept (Eylea<sup>®</sup>) therapy using a proactive treat-and-extend regimen in neovascular age-related macular degeneration**

### **Ninety-six-week results of the ALTAIR study, a randomized clinical trial**

---

This publication has been produced on behalf of Bayer and presents 96-week findings from ALTAIR (ClinicalTrials.gov NCT02305238), a randomized clinical trial in Japanese patients with neovascular age-related macular degeneration that assessed the efficacy and safety of intravitreal aflibercept (Eylea<sup>®</sup>, Bayer/Regeneron) therapy following two different adjustment intervals (2-week and 4-week) of a treat-and-extend dosing regimen.<sup>1</sup> Medical writing support was provided by Rod McNeil Associates and was funded by Bayer.

Prescribing information for aflibercept solution for injection can be found on the last page.



# Aflibercept T&E in neovascular age-related macular degeneration

## PREFACE

The licensed posology of intravitreal aflibercept injection (Eylea®, Bayer/Regeneron) for neovascular age-related macular degeneration (nAMD) allows the flexibility of either bimonthly dosing or proactive treat-and-extend (T&E) dosing beyond every 8 weeks (q8) after initial loading with 3 monthly doses.<sup>2</sup>

Supporting evidence for earlier treatment extension came from the ALTAIR study, which demonstrated excellent visual outcomes through 96 weeks using aflibercept T&E dosing, with more than 40% of patients achieving a last injection interval of 16 weeks and up to 60% achieving a treatment interval of 12 weeks or longer.<sup>1</sup> The 52- and 96-week data for the ALTAIR study are presented and discussed in this publication.

## ALTAIR OVERVIEW

**Significance:** Prior to ALTAIR, no randomized controlled studies have examined in detail the anti-vascular endothelial growth factor (VEGF) treatment outcomes associated with 4-week interval adjustments and variable extended dosing up to a 4-month maximum interval in patients with nAMD.

**Purpose:** To determine the efficacy and safety of intravitreal aflibercept injection (IAI) therapy using a T&E regimen following two different interval adjustments in treatment-naïve patients with nAMD for up to 96 weeks.

**Study design:** ALTAIR (n=246, 123 in each group) was a 96-week, randomized, open-label, parallel assignment phase 4 study of aflibercept for nAMD using a protocol-defined T&E regimen following 2-week [IAI T&E-2W] or 4-week [IAI T&E-4W] interval adjustments, after a loading phase, up to a maximum injection interval of 16 weeks and a minimum of 8 weeks.

**Main outcome measure:** Mean change in best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline to week 52.

**Results:** Mean (SD) age was 74.0 (8.0) years, mean (SD) baseline BCVA was 55.0 (12.5) letters and a majority (72.4%) were male. Mean BCVA gains from baseline were 9.0 and 8.4 letters at week 52 and 7.6 and 6.1 letters at week 96, in the IAI T&E-2W and IAI T&E-4W groups, respectively. Mean change in central retinal thickness from baseline was -134.4 µm and -126.1 µm at week 52 and -130.5 µm and -125.3 µm at week 96. The proportion of patients without retinal fluid on optical coherence tomography was 67.5% in both treatment arms at week 96. The proportions of patients maintaining vision (losing <15 letters) were 96.7% and 95.9% at week 52 and 95.1% and 91.9% at week 96. There was a gain of 15 or more letters in 32.5% and 30.9% of patients at week 52 and 31.7% and 28.5% at week 96. Patients in each group received on average 10.4 injections through 96 weeks, with a mean of 3.6 and 3.7 injections respectively from weeks 52 to 96. The mean (SD) last treatment interval at week 96 was 12.2 (3.6) weeks in the IAI T&E-2W group and 12.5 (3.6) weeks in the IAI T&E-4W group. At final study visit, 57–60% of ALTAIR participants had a last injection interval of 12 weeks or more and greater than 40% had a last injection interval of 16 weeks. No unexpected safety signals were identified with intravitreal aflibercept.

**Conclusion:** Improvements in functional and anatomic outcomes were maintained through 96 weeks of T&E dosing using aflibercept, with a marked reduction in treatment frequency in the second year.

# Findings from ALTAIR, a ninety-six-week study of treat-and-extend aflibercept therapy in neovascular AMD

## The ALTAIR investigators

### INTRODUCTION

The treatment goal of intravitreal anti-VEGF therapy in nAMD is to maximize and maintain functional and anatomic outcomes while minimizing treatment frequency and clinic visits long term.<sup>3</sup> Anti-VEGF maintenance therapy for nAMD using a flexible T&E strategy may help to balance the risk of visual decline from undertreatment with a personalized retreatment schedule based on individual visual and anatomic responses.<sup>3,4</sup>

While T&E after a loading phase of monthly treatment is the preferred anti-VEGF dosing strategy of choice for many clinicians,<sup>5</sup> the optimal T&E regimen and retreatment algorithm for nAMD in real-world clinical practice has yet to be determined. Also, there is limited evidence available addressing the question of how intervals for treating and monitoring differ among subjects and how retreatment criteria are best applied to achieve good outcomes in real-life practice.

The molecular properties of aflibercept allow potentially for extended injection intervals. Previous studies of aflibercept in nAMD have reported a median aqueous half-life of 11 days<sup>6</sup> and a range of intraocular VEGF suppression times of up to 16 weeks.<sup>7,8</sup> Further, the binding affinity of aflibercept to VEGF is substantially greater than other intraocular anti-VEGF agents.<sup>9</sup> As the duration of VEGF suppression varies between patients and therapies,<sup>7,10</sup> customizing the dosing regimen to individual patients based on functional and anatomic evaluations ensures optimal outcomes and removes the need for interim monitoring.<sup>3</sup>

ALTAIR is the first randomized controlled trial to provide large-scale, prospective clinical data exploring outcomes and interval adjustments using proactive T&E dosing with aflibercept for patients with nAMD. Prior to ALTAIR, no randomized controlled studies have examined in detail the anti-VEGF treatment outcomes associated with 4-week interval adjustments and extended dosing beyond every 8 weeks up to a 4-month maximum treatment interval. Another interesting feature of ALTAIR was the protocol-defined criteria for maintenance of treatment intervals if there was residual but decreased fluid and no sign of progressive or recurrent disease activity (i.e., no vision loss  $\geq 5$  ETDRS letters, no increase in central retinal thickness [CRT]  $\geq 100$   $\mu\text{m}$ , no new neovascularization and/or no new macular hemorrhage).

### EXPLORING ALTAIR

ALTAIR investigators examined the efficacy and safety of aflibercept therapy administered in two different T&E regimens (2-week

and 4-week adjustments) in treatment-naïve patients with nAMD, up to a maximum treatment interval of 16 weeks and dosing no more frequently than every 8 weeks (ClinicalTrials.gov NCT02305238). The trial was conducted between December 2014 and November 2017 and involved 41 centers across Japan.

**TABLE 1. Eligibility criteria.**

#### Inclusion criteria:

- Japanese men and women  $\geq 50$  years of age
- Active primary subfoveal CNV lesions secondary to nAMD, including juxtafoveal lesions that affect the fovea as evidenced by fluorescein angiography in the study eye
- ETDRS BCVA of 73 to 25 letters (approximately 20/40 to 20/320 Snellen equivalent) in the study eye

#### Exclusion criteria:

- Prior treatment of the study eye with intraocular anti-VEGF agents, verteporfin (PDT), other laser, intraocular corticosteroids, surgical interventions (except cataract surgery more than 30 days prior to screening) or systemic use of anti-VEGF products within 3 months prior to study entry
- Active or suspected infection in or surrounding of the study eye
- Active severe intraocular inflammation in the study eye
- IOP  $\geq 25$  mmHg in the study eye
- Ocular condition in the study eye which may impact vision and confound study outcomes
- History of allergy to aflibercept or allergy to study/treatment-related agents, including fluorescein, indocyanine green, povidone iodide, lidocaine, or antibiotic eye drops
- Women who are pregnant or lactating, or suspected to be pregnant
- Previous enrolment into the run-in phase of this study
- Previous (within 3 months) or concomitant participation in another clinical study with investigational medicinal product(s)
- Close affiliation with the investigational site, e.g., a close relative of the investigator or dependent person (e.g., an employee or a student of the investigational site)
- Patients who the investigator deemed to be ineligible for the study

nAMD, neovascular age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.  
Source: Ohji M, et al. *Adv Ther.* 2020.

## Study design and methods

### Participants, randomization and interventions

Inclusion and exclusion criteria were similar to those of the pivotal VIEW phase 3 randomized clinical trials (TABLE 1). All patients received three initial monthly injections. At week 16, patients received aflibercept and were randomized 1:1 to receive aflibercept in a T&E regimen with either a 2-week or 4-week adjustment (FIGURE 1). Following randomization, the treatment interval could be gradually extended, shortened or maintained based on visual and/or anatomic criteria defined by protocol with a maximum interval of 16 weeks and a minimum interval of 8 weeks for both groups (FIGURE 2).

Patients meeting the criteria for treatment adjustment had their injection interval extended or shortened by either 2 weeks or 4 weeks. In the IAI T&E-4W arm, when a participant met criteria for interval shortening, any subsequent extension was limited to 2-week adjustments. Patients in the IAI T&E-4W arm who had their interval shortened remained in the 4-week group for data analysis.

### Study endpoints and analysis

Outcomes were assessed at weeks 52 and 96. The primary endpoint was mean change from baseline in BCVA at week 52, measured as ETDRS letter score. Secondary outcome measures included:

- proportion of patients who maintained vision (losing fewer than 15 letters compared to baseline);
- proportion of patients who gained at least 15 letters of vision compared with baseline;
- mean change in CRT from baseline;
- proportion of patients without fluid on optical coherence tomography (OCT);

- treatment exposure, including mean number of injections, mean injection interval, last injection interval and next intended injection interval; and
- safety and tolerability.

### Ophthalmic assessments

Ophthalmic assessments, conducted at every treatment and evaluation visit, except for safety follow-up, involved visual acuity testing with ETDRS letter score, slit lamp and indirect ophthalmoscopy and OCT. Fundus photography, fluorescein angiography and indocyanine green angiography were conducted at the screening visit and at weeks 52 and 96.

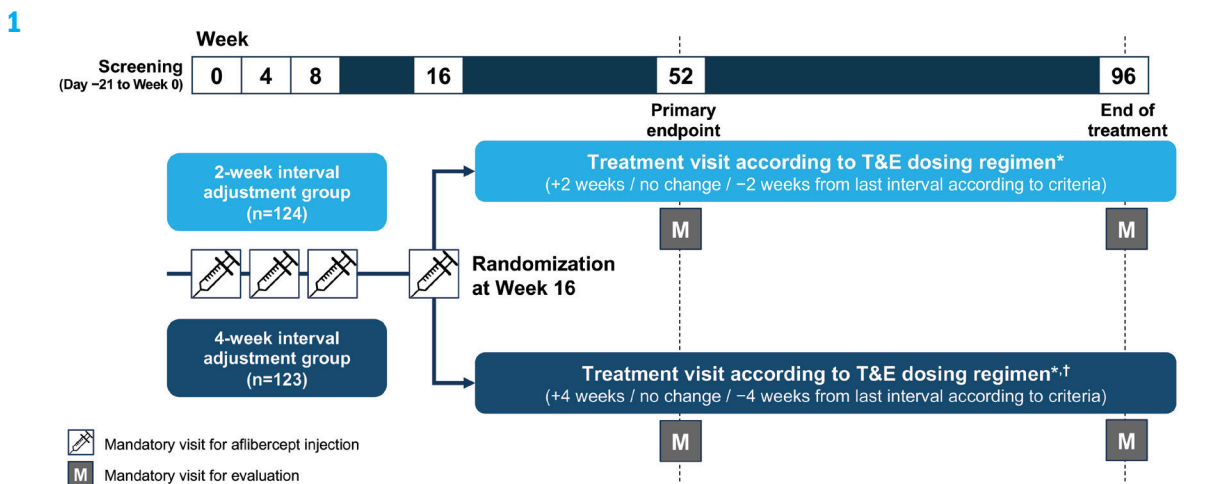
## Findings from ALTAIR

### Patient disposition and baseline characteristics

In total, 124 patients were randomized to the IAI T&E-2W group and 123 patients to the IAI T&E-4W group. Baseline demographics and clinical characteristics were evenly balanced across the two treatment arms (TABLE 2). More than one third of patients had polypoidal choroidal vasculopathy (36.6%) and the proportion of patients with retinal angiomatous proliferation lesions was low (5.3%). One patient in the IAI T&E-2W group was not included in the full analysis set due to discontinuation immediately after randomization. Overall, 85.8% (n = 212) completed the study. Reasons for discontinuation included progressive disease (n = 8), withdrawal by patient (n = 7) and adverse events (n = 6).

### Primary endpoint outcome

- Mean BCVA gains were 9.0 letters (95% CI, 6.4–11.5) and 8.4 letters (95% CI, 6.0–10.8) at week 52 (least squares [LS] mean difference of -0.4 [95% CI, -3.8 to 3.0]) in the IAI T&E-2W and IAI T&E-4W groups, respectively



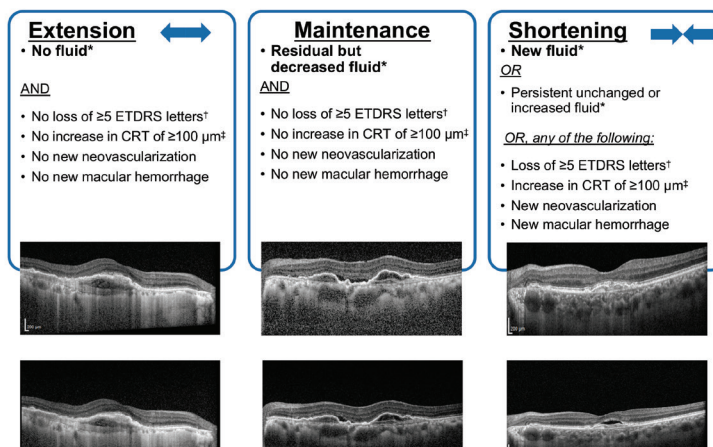
\*The minimum treatment interval was 8 weeks and the maximum treatment interval was 16 weeks; the decision to adjust the treatment interval was based on the T&E regimen criteria, assessed by OCT.  
 †Re-extension after shortening the intervals and subsequent re-shortening after extending the intervals were adjusted by 2 weeks.  
 nAMD, neovascular age-related macular degeneration; OCT, optical coherence tomography; T&E, treat-and-extend.  
 Adapted from Ohji M, et al. Adv Ther. 2020.

(FIGURE 1). ALTAIR study design.

### Minimum and maximum intervals (Weeks 16–96):

**Minimum interval:  
8 weeks**

**Maximum interval:  
16 weeks**



\*Decision was based on the T&E regimen criteria, assessed by OCT. †Loss of ≥5 ETDRS letters from the last treatment visit in conjunction with recurrent fluid on OCT.  
‡Increase in CRT of ≥100 μm compared with the lowest previous value assessed by OCT.  
CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; T&E, treat-and-extend.  
Ohji M, et al. Presentation at the 18th European Society of Retina Specialists (EURETINA) Congress; Vienna, Austria, September 20–23, 2018.

(FIGURE 2. Afibercept T&E regimen guided by specific criteria for extension, maintenance and shortening of dosing interval.

#### Other functional outcomes:

- At week 96, mean BCVA gains were 7.6 letters (95% CI, 5.0–10.3) and 6.1 letters (95% CI, 3.1–9.0) at week 96 (LS mean difference of -1.4 [95% CI, -5.3 to 2.4]) (FIGURE 3).
- The proportion of patients maintaining visual acuity (losing < 15 letters) was 96.7% (95% CI, 93.6–99.9) and 95.9% (95% CI, 92.4–99.4) at week 52 (Mantel-Haenszel [MH]-adjusted difference of -0.9% [95% CI, -5.7 to 4.0]), and 95.1% (95% CI, 91.3–98.9) and 91.9% (95% CI, 87.0–96.7) at week 96 in the IAI T&E-2W and IAI T&E-4W groups, respectively (MH-adjusted difference of -3.1% [95% CI, -9.5 to 3.2]) (FIGURE 4).
- The proportion of patients gaining at least 15 ETDRS letters was 32.5% (95% CI, 24.2–40.8) and 30.9% (95% CI, 22.7–39.1) at week 52 (MH-adjusted difference of -1.4% [95% CI, -12.7 to 9.8]), and 28.5% (95% CI, 20.5–36.4) and 31.7% (95% CI, 23.5–39.9) at week 96 in the IAI T&E-2W and IAI T&E-4W groups, respectively (MH-adjusted difference of 3.4% [95% CI, -7.9 to 14.7]) (FIGURE 5).

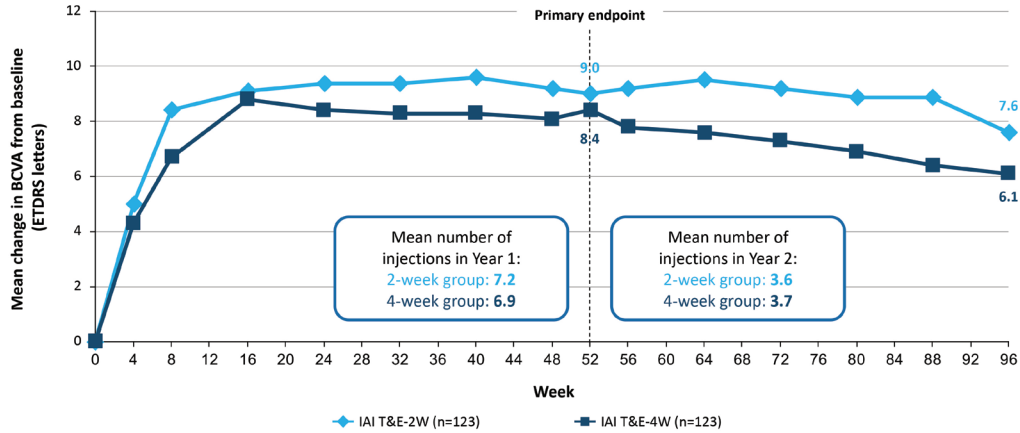
**TABLE 2. Patient baseline characteristics and demographics (FAS).**

Characteristic	IAI T&E-2W n=123	IAI T&E-4W n=123	Total n=246
Age, mean (SD), years	73.0 (7.9)	75.0 (8.1)	74.0 (8.0)
Sex, n (%)			
Male	87 (70.7)	91 (74.0)	178 (72.4)
Baseline BCVA score, mean (SD)	54.8 (13.1)	55.3 (12.0)	55.0 (12.5)
Baseline CRT, mean (SD), μm	386.2 (159.2)	370.3 (120.0)	378.3 (141.0)
Type of exudative AMD, n (%)*			
Typical AMD	75 (61.0)	75 (61.0)	150 (61.0)
Polypoidal choroidal vasculopathy	46 (37.4)	44 (35.8)	90 (36.6)
Retinal angiomatous proliferation	4 (3.3)	9 (7.3)	13 (5.3)
Type of CNV lesions on FA, n (%)†			
Classic CNV	35 (28.5)	42 (34.1)	77 (31.3)
Classic CNV and occult CNV	14 (11.4)	17 (13.8)	31 (12.6)
Occult CNV	72 (58.5)	62 (50.4)	134 (54.5)
Pigment epithelial detachment, n (%)	83 (67.5)	78 (63.4)	161 (65.4)
Subretinal fluid, n (%)	104 (84.6)	104 (84.6)	208 (84.6)
Intraretinal fluid, n (%)	43 (35.0)	44 (35.8)	87 (35.4)
Hemorrhage, n (%)			
Subretinal hemorrhage	67 (54.5)	61 (49.6)	128 (52.0)
Intraretinal hemorrhage	56 (45.5)	50 (40.7)	106 (43.1)
Intraretinal hemorrhage	28 (22.8)	30 (24.4)	58 (23.6)

\*Patients could be classified into more than one group. †Unknown in the IAI T&E-2W (n = 2) and IAI T&E-4W (n = 1) adjustment groups and one patient had no CNV in the IAI T&E-4W group. 2W/4W, 2-/4-week adjustment; AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness; FA, fluorescein angiography; FAS, full analysis set; IAI, intravitreal aflibercept injection; SD, standard deviation; T&E, treat-and-extend.

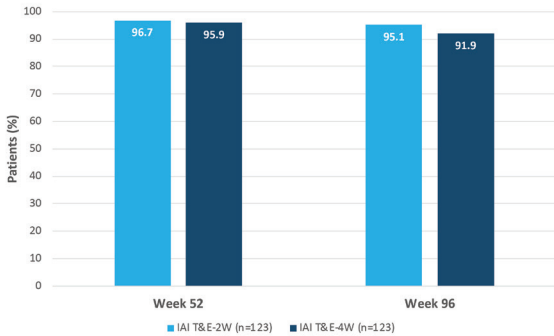
Source: Ohji M, et al. Adv Ther. 2020.

3



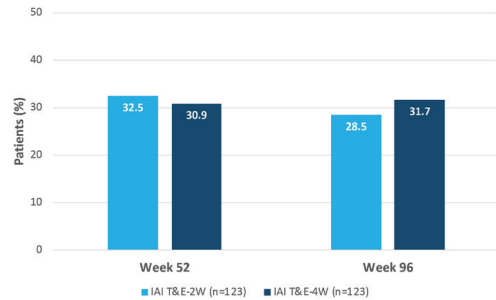
Full analysis set; last observation carried forward. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; T&E, treat-and-extend; 2W/4W, 2-/4-week adjustment. Adapted from Ohji M, et al. Adv Ther. 2020.

4



Last observation carried forward analysis. BCVA, best-corrected visual acuity; FAS, full analysis set; IAI, intravitreal aflibercept injection; T&E, treat-and-extend; 2W/4W, 2-/4-week adjustment. Adapted from Ohji M, et al. Adv Ther. 2020.

5



Last observation carried forward analysis. ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; T&E, treat-and-extend; 2W/4W, 2-/4-week adjustment. Adapted from Ohji M, et al. Adv Ther. 2020.

(FIGURE 3. Mean change in BCVA in IAI T&E-2W and IAI T&E-4W groups from baseline to week 96 (FAS). 4. The proportion of patients losing <15 ETDRS letters. 5. The proportion of patients gaining ≥15 ETDRS letters.

**Anatomic outcomes**

- The mean change in CRT from baseline to week 52 was -134.4 μm (95% CI, -162.2 to -106.6) in the IAI T&E-2W group and -126.1 μm (95% CI, -147.1 to -105.1) in the IAI T&E-4W group (LS mean difference of -5.8 μm [95% CI, -24.3 to 12.7]). From baseline to week 96, mean change in CRT was -130.5 μm (95% CI, -158.7 to -102.4) in the IAI T&E-2W group and -125.3 μm (95% CI, -146.6 to -104.1) in the IAI T&E-4W group (LS mean difference of -9.0 [95% CI, -27.7 to 9.7]) (FIGURE 6).
- The proportion of patients without retinal fluid at week 16

was 53.7% (IAI T&E-2W) and 62.6% (IAI T&E-4W), and 68.3% (95% CI, 60.1–76.5) (IAI T&E-2W) and 69.1% (95% CI, 60.9–77.3) (IAI T&E-4W) at week 52 (MH-adjusted difference of -1.0% [95% CI, -10.6 to 12.7]). At week 96, 67.5% (95% CI, 59.2–75.8) of patients in both arms had no fluid on OCT (MH-adjusted difference of 0.4% [95% CI, -11.4 to 12.2]).

**Treatment exposure**

- TABLE 3 summarizes the mean number of injections, mean last injection interval and proportions achieving extended



intervals of 12 weeks and beyond at weeks 52 and 96.

- The last injection interval before week 96 was at least 12 weeks in 56.9% (IAI T&E-2W) and 60.2% (IAI T&E-4W) and more than 40% of patients (41.5% and 46.3%, respectively) reached a last injection interval of 16 weeks (FIGURE 7).
- The proportion of patients extended to a 16-week injection interval and maintained at this interval until study completion was 41.5% in the IAI T&E-2W group and 42.3% in the IAI T&E-4W group.
- Up to week 96, the proportion of patients extended to treatment intervals of 12 weeks and beyond who maintained a quarterly or longer treatment interval was 48.0% for both treatment arms.
- The proportion of patients maintained on a treatment interval of 8 weeks with no extension was 27.6% and 22.0% in the IAI T&E-2W and IAI T&E-4W groups, respectively.

### Safety

Adverse event findings were consistent with the known safety profile for aflibercept. The proportion of treatment-emergent adverse events (TEAEs) was comparable between treatment arms and these were predominantly mild and moderate in severity. The most common ocular TEAEs in the IAI T&E-2W and IAI T&E-4W groups, respectively, were cataract (5.6% and 8.1%), conjunctival hemorrhage (3.2% and 6.5%), dry eye (2.4% and 4.9%) and retinal pigment epithelium tear (2.4% and 0%), while the most common non-ocular TEAEs were nasopharyngitis (21.0% and 16.3%) and constipation (3.2% and 5.7%). The overall incidences of ocular TEAEs and serious adverse events were similar between the two T&E arms. The proportion of Antiplatelet Trialists' Collaboration (APTCC)-de-

finied arterial thromboembolic events was similar between treatment arms (0.8% and 1.6%) and consistent with previous studies.<sup>11,12</sup> Three patients (one in the IAI T&E-2W group and two in the IAI T&E-4W group) discontinued therapy due to a TEAE up to week 96.

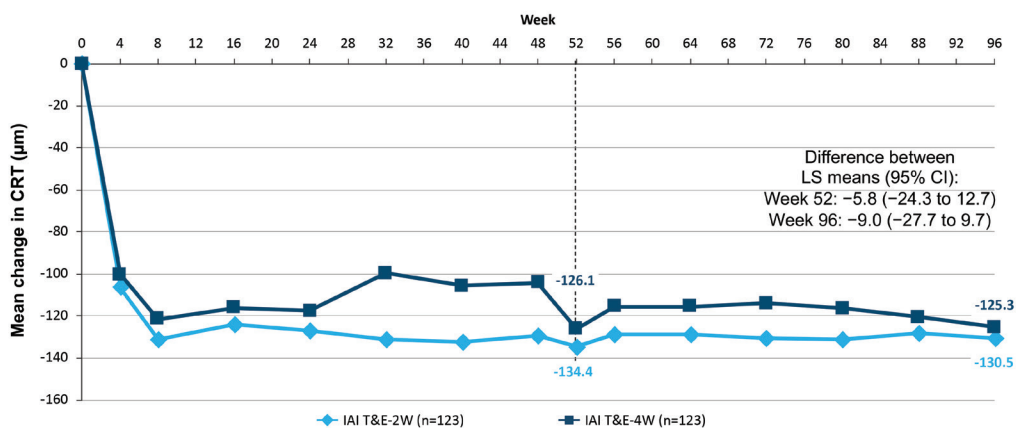
### Discussion

Over the course of the ALTAIR study, clinically relevant vision gains achieved through 52 weeks of aflibercept T&E therapy were maintained through to the end of the study at week 96. On average, patients gained at least 8 letters of visual acuity from baseline to week 52 and improvements in vision were comparable between treatment groups. Vision gains were essentially upheld until the end of the study. The mean number of injections received by patients over 52 weeks was similar between treatment arms. More than half of patients (57-58%) had a next intended treatment interval of 12 weeks or greater up to week 52 (defined as the time between the last injection and the next scheduled injection at the time of study visit).

Vision gains achieved in year 1 were maintained through week 96 with fewer than 4 injections in year 2 and the mean number of injections over the course of the study was the same in the two treatment arms (10.4).

The mean change in BCVA observed in the IAI T&E-4W arm was similar to that of the IAI T&E-2W arm. Around one third in each treatment group gained 15 or more letters at weeks 52 and 96 (30.9-32.5% week 52 and 28.5-31.7% week 96). Reductions in CRT achieved in the first year were maintained to week 96 and reductions in CRT from baseline were similar between treatment arms. Almost 70% of patients were fluid free on OCT at weeks 52 and 96 (68.3-69.1% and 67.5%, respectively).

6



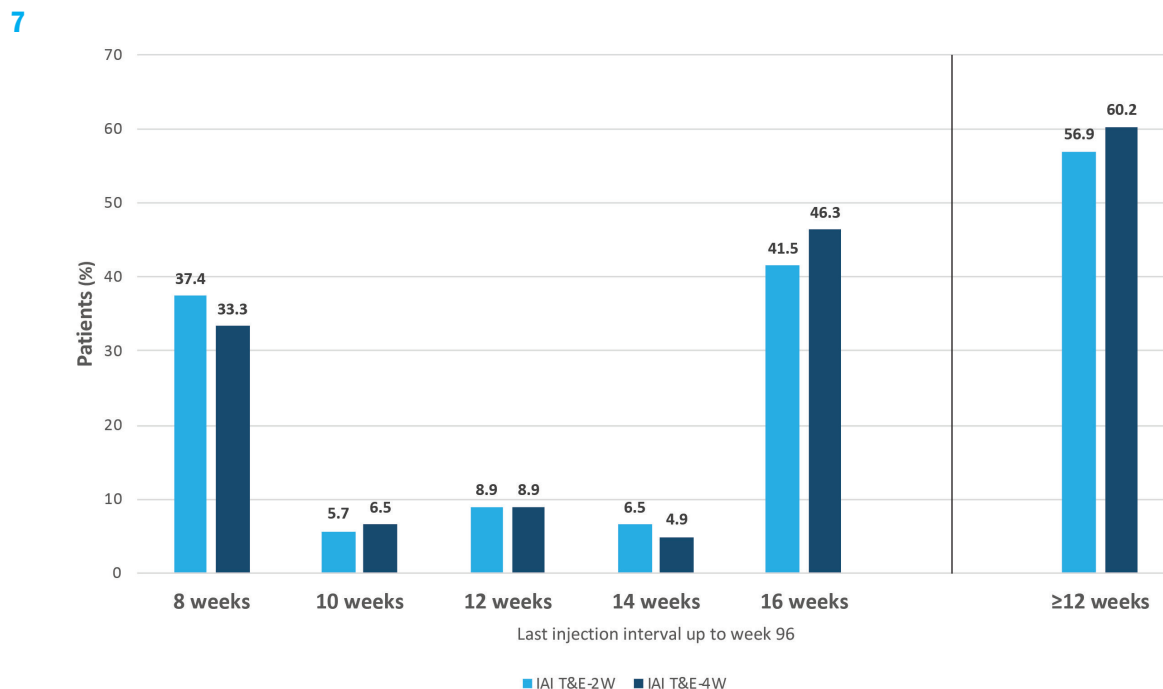
Full analysis set; last observation carried forward. CI, confidence interval; CRT, central retinal thickness; IAI, intravitreal aflibercept injection; LS, least squares; T&E, treat-and-extend; 2W/4W, 2-/4-week adjustment. Adapted from Ohji M, et al. *Adv Ther*. 2020.

(FIGURE 6. Mean change in central retinal thickness from baseline to week 96 (FAS).

**TABLE 3.** Number of injections, mean last injection interval and proportion reaching an injection interval of ≥12 weeks at weeks 52 and 96.

Treatment exposure	Aflibercept T&E regimen Week 52 <sup>a</sup>		Aflibercept T&E regimen Week 96 <sup>a</sup>	
	IAI T&E-2W (n=123)	IAI T&E-4W (n=123)	IAI T&E-2W (n=123)	IAI T&E-4W (n=123)
Mean (SD) number of injections from baseline	7.2 (0.9)	6.9 (1.0)	10.4 (2.6)	10.4 (2.4)
Mean (SD) number of injections from weeks 52 to 96			3.6 (1.6)	3.7 (1.4)
Mean (SD) last injection interval, weeks	10.7 (2.7)	11.8 (3.7)	12.2 (3.6)	12.5 (3.6)
Proportion with last injection interval ≥12 weeks, %	42.3	49.6	56.9	60.2
Proportion with last injection interval of 16 weeks, %	0.0	40.7	41.5	46.3

IAI, intravitreal aflibercept injection; SD, standard deviation; T&E, treat-and-extend; 2W/4W, 2-/4-week adjustment. Adapted from Ohji M, *et al.* Adv Ther. 2020.



IAI, intravitreal aflibercept injection; T&E, treat-and-extend; 2W/4W, 2-/4-week adjustment. Adapted from Ohji M, *et al.* Adv Ther. 2020.

**(FIGURE) 7.** Distribution of last injection interval before week 96 with aflibercept T&E using two different interval adjustments.



**TABLE 4. Efficacy outcomes at week 52 (primary analysis) and week 96 from the ALTAIR study, combined efficacy data from the VIEW studies included for reference.**

Outcome measure	Aflibercept T&E regimen Week 52 <sup>a</sup>		Aflibercept T&E regimen Week 96 <sup>a</sup>		VIEW studies IAI 2Q8 <sup>b,c</sup>	
	IAI T&E-2W (n=123)	IAI T&E-4W (n=123)	IAI T&E-2W (n=123)	IAI T&E-4W (n=123)	Week 52	Week 96
					(n=607)	
Mean change from baseline in BCVA, ETDRS letter score	9.0	8.4	7.6	6.1	8.4	7.62
Mean change in CRT from baseline, µm	-134.4	-126.1	-130.5	-125.3	-139	-133
Proportion gaining ≥15 ETDRS letters from baseline, %	32.5	30.9	28.5	31.7	30.97	33.44
Mean number of injections from baseline	7.2	6.9	10.4	10.4	7.0	11.2
Mean number of injections from weeks 52 to 96*			3.6	3.7		4.2
Proportion without fluid on OCT, %	68.3	69.1	67.5	67.5	67.7	50.1
Proportion maintaining vision (losing <15 ETDRS letters), %	96.7	95.9	95.1	91.9	95.33	92.42

BCVA, best-corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; OCT, optical coherence tomography; SD, standard deviation; T&E, treat-and-extend; 2Q8, 2 mg aflibercept every 8 weeks following 3 monthly doses in year one and capped as-needed treatment (requiring at least quarterly dosing) from weeks 52 to 96; 2W/4W, 2-/4-week adjustment.

\* Subjects who completed week 52, n=116 and n=111 for IAI T&E-4W and IAI T&E-2W groups, respectively.

<sup>a</sup>Ohji M, *et al.* Adv Ther. 2020.

<sup>b</sup>Heier JS, *et al.* Ophthalmology. 2012.

<sup>c</sup>Schmidt-Erfurth, *et al.* Ophthalmology. 2014.

Up to 60% (56.9-60.2%) of participants were extended to quarterly or longer injection intervals and close to half of the study population reached an extended interval of 16 weeks at the last study visit. Overall, 85.9% of those who reached the maximum possible treatment interval of 16 weeks at the end of year 1 were maintained at this interval through to week 96 (96.3% in the IAI T&E-2W group and 77.6% in the IAI T&E-4W group).

#### T&E offers benefits to both physicians and patients

Decreased treatment burden is acknowledged as an important unmet need in the management of nAMD.<sup>13</sup> ALTAIR investigators noted that utilization of a proactive aflibercept T&E regimen, further substantiated by the results of ALTAIR, allows for a pragmatic approach to the treatment of nAMD.<sup>1</sup> Individualized T&E dosing regimens minimize the need for interim monitoring; furthermore, treating at each visit and planning the next injection minimizes the possibility of treatment delays and facilitates clinic management.<sup>1</sup>

ALTAIR results show that, over 96 weeks of treatment, good functional outcomes are achievable using a T&E regimen with a minimum injection interval of 8 weeks. Functional (BCVA improvement and vision maintenance) and anatomic (CRT reduction and fluid resolution) outcomes in ALTAIR are comparable to those observed for aflibercept administered every month or every 2 months after 3 monthly injections in the phase 3 VIEW registration studies, despite fewer injections (10.4, 16.0

[q4] and 11.2 [q8], respectively) (TABLE 4).<sup>11,12</sup> Of note, close to half (48%) of patients initiated on aflibercept q8 treatment in the VIEW studies maintained vision with quarterly dosing in the second year.<sup>14</sup>

Extending treatment intervals by 4-week increments, as well as extending when appropriate up to a maximum 16-week treatment interval and maintaining treatment intervals in the presence of some residual fluid, offers potential advantages for both patients (e.g., reduced treatment and visit frequency) and health-care providers (e.g., more predictable scheduling approach that may aid service capacity planning).<sup>3,15,16</sup> In other T&E studies, protocols were based on extending or shortening using 2-week interval adjustments, with a minimum interval of 4 weeks and a maximum extension interval of 12 weeks only.<sup>17-19</sup>

Results from ALTAIR indicate that aflibercept injection intervals can be extended to 12 weeks and beyond in many patients. Other prospective studies of ranibizumab and aflibercept T&E regimens have reported extensions to quarterly dosing intervals in 17-37% of patients.<sup>17,20-22</sup>

Two-year results from the ARIES study (n = 210) provide further evidence supporting the effectiveness of a T&E schedule using aflibercept in nAMD. Good visual acuity improvements were achieved with a mean of 12.0 injections through 104 weeks. More than half of patients were extended to injection intervals of 12 weeks or beyond and up to a third extended to injection intervals of 16 weeks by the end of year 2.<sup>23</sup>

### *A practical and personalized approach can secure robust outcomes in nAMD*

A T&E regimen, guided by anatomic and visual acuity outcomes, provides a practical and personalized approach to securing effective maintenance therapy in nAMD, helping avoid under-treatment of active CNV while minimizing injection frequency. Applied appropriately, a T&E schedule represents a manageable treatment pathway that addresses individual patient needs and helps to minimize disease recurrence.<sup>3,4</sup>

Tailoring treatment frequency to meet individual patient needs further eases the burden of injections and clinic visits for those who respond particularly well early on. Moreover, visual results achieved using a T&E regimen in nAMD approach those observed using fixed monthly or bimonthly dosing regimens and are superior to those seen with as-needed dosing.<sup>19,24,25</sup>

### **BOTTOM LINE**

ALTAIR study investigators concluded that aflibercept T&E for nAMD improved and maintained functional and anatomic outcomes over 96 weeks, while minimizing treatment exposure. A T&E dosing regimen with aflibercept in nAMD, following initial monthly dosing, allows extended dosing beyond every 8 weeks up to a 16-week maximum injection interval, with flexibility to adjust intervals by 2-week or 4-week increments to maintain stable visual and/or anatomic outcomes. This approach offers the potential to reduce the treatment burden and the risks associated with frequent intravitreal injections.<sup>26</sup> Future studies are expected to provide further insights into potential predictive factors (such as fluid status and lesion subtype) of treatment outcomes and required injection intervals when using an aflibercept T&E regimen for patients with nAMD.

### **TAKE-HOME MESSAGES**

- Intravitreal aflibercept therapy given using a proactive T&E regimen up to a 16-week maximum injection interval for treatment-naïve nAMD improved functional (BCVA gain 9.0 and 8.4 letters) and anatomic outcomes (CRT reduction 134.4  $\mu\text{m}$  and 126.1  $\mu\text{m}$ ) at 52 weeks and outcomes were maintained to week 96 with fewer injections over time.
- T&E dosing with 2-week or 4-week interval adjustments earlier in the first year of aflibercept treatment achieves excellent visual outcomes and may reduce the burden of treatment in terms of injection frequency and clinic visits for many patients:
  - at year 1, 57% of patients had a next intended injection interval  $\geq 12$  weeks and a large proportion (35.1% and 40.5%) had a next intended injection interval of 16 weeks;
  - up to 96% of patients who reached the maximum possible treatment interval of 16 weeks at the end of year 1 were maintained at this interval to week 96; and
  - before week 96, up to 60% of patients had a last injection interval of at least 12 weeks and more than 40% reached the 16-week maximum injection interval.
- Vision outcomes of aflibercept T&E for nAMD were comparable to those observed for aflibercept administered monthly or every 2 months after loading in the VIEW studies and superior to those seen with as-needed dosing.<sup>12,19,24,25</sup>

## REFERENCES

1. Ohji M, Takahashi K, Okada AA, et al. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52- and 96-week findings from ALTAIR. *Adv Ther*. 2020;37(3):1173-1187.
2. Eylea® 40 mg/ml solution for injection in a vial - summary of product characteristics. Leverkusen, Germany: Bayer AG; 2018. Available at: <https://www.medicines.org.uk/emc/medicine/27224>.
3. Lanzetta P, Loewenstein A; Vision Academy Steering Committee. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(7):1259-1273.
4. Freund KB, Korobelnik JF, Devenyi R, et al. Treat-and-extend regimens with anti-VEGF agents in retinal diseases: a literature review and consensus recommendations. *Retina*. 2015;35(8):1489-506.
5. Stone TW, ed. ASRS 2017 Preferences and Trends Membership Survey: Chicago, IL. American Society of Retina Specialists; 2017.
6. Do DV, Rhoades W, Nguyen QD. Pharmacokinetic study of intravitreal aflibercept in humans with neovascular age-related macular degeneration. *Retina*. 2020;40(4):643-647.
7. Fauser S, Schwabecker V & Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. *Am J Ophthalmol*. 2014;158:532-536.
8. Fauser S, Muether PS. Clinical correlation to differences in ranibizumab and aflibercept vascular endothelial growth factor suppression times. *Br J Ophthalmol*. 2016;100(11):1494-1498.
9. 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(2):171-85.
10. Mantel I, Deli A, Iglesias K, Ambresin A. Prospective study evaluating the predictability of need for retreatment with intravitreal ranibizumab for age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2013;251(3):697-704.
11. Heier JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119:2537-48.
12. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121:193-201.
13. Singh RP, Stone TW, eds. 2018 Global Trends in Retina Survey: Chicago, IL. American Society of Retina Specialists; 2018.
14. Richard G, Monés J, Wolf S, et al. Scheduled versus pro re nata dosing in the VIEW Trials. *Ophthalmology*. 2015;122(12):2497-503.
15. Koh A, Lanzetta P, Lee WK, et al. Recommended guidelines for use of intravitreal aflibercept with a treat-and-extend regimen for the management of neovascular age-related macular degeneration in the Asia-Pacific region: Report from a consensus panel. *Asia Pac J Ophthalmol (Phila)*. 2017;6:296-302.
16. Ross AH, Downey L, Devonport H, et al. Recommendations by a UK expert panel on an aflibercept treat-and-extend pathway for the treatment of neovascular age-related macular degeneration. *Eye (Lond)*. 2020 Jan 3. doi: 10.1038/s41433-019-0747-x. [Epub ahead of print]
17. Berg K, Hadzalic E, Gjertsen I, et al. Ranibizumab or bevacizumab for neovascular age-related macular degeneration according to the Lucentis compared to Avastin study treat-and-extend protocol: Two-year results. *Ophthalmology*. 2016;123:51-59.
18. Yamamoto A, Okada AA, Nakayama M, et al. One-year outcomes of a treat-and-extend regimen of aflibercept for exudative age-related macular degeneration. *Ophthalmologica*. 2017;237(3):139-144.
19. Silva R, Berta A, Larsen M, et al; TREND Study Group. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. *Ophthalmology*. 2018;125(1):57-65.
20. Wykoff CC, Ou WC, Brown DM, et al; TREX-AMD Study Group. Randomized trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: 2-year results of the TREX-AMD study. *Ophthalmol Retina*. 2017;1(4):314-321.
21. Gillies MC, Hunyor AP, Arnold JJ, et al. Effect of ranibizumab and aflibercept on best-corrected visual acuity in treat-and-extend for neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol*. 2019;137(4):372-379.
22. Guymer RH, Markey CM, McAllister IL, et al; FLUID Investigators. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: FLUID study 24-month results. *Ophthalmology*. 2019;126(5):723-734.
23. Mitchell P, Souied E, Midena E, et al. Efficacy of intravitreal aflibercept administered using a treat-and-extend regimen over 2 years in patients with neovascular age-related macular degeneration: ARIES results. Presentation at the 19th European Society of Retina Specialists (EURETINA) Congress; Paris, France, September 5-8, 2019.
24. Adrean SD, Chaili S, Ramkumar H, et al. Consistent long-term therapy of neovascular age-related macular degeneration managed by 50 or more anti-VEGF injections using a treat-extend-stop protocol. *Ophthalmology*. 2018;125(7):1047-1053.
25. Rofagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmol*. 2013;120:2292-2299.
26. Sarwar S, Clearfield E, Soliman MK, et al. Aflibercept for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2016 Feb 8;2:CD011346.





**Name of the medicinal product:** Eylea 40mg/ml solution for injection in prefilled syringe. Eylea 40 mg/ml solution for injection in a vial. (Refer to full SmPC before prescribing.) **Composition:** One prefilled syringe contains 90 µl, equivalent to 3.6 mg aflibercept. Each vial contains 100 µl, equivalent to 4 mg aflibercept. Excipients: Polysorbate 20, Sodium dihydrogen phosphate, monohydrate, Disodium hydrogen phosphate, heptahydrate, Sodium chloride, Sucrose, Water for injection. **Indication:** Eylea is indicated for adults for treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DME) and visual impairment due to myopic choroidal neovascularisation (myopic CNV). **Administration and Dosage:** For intravitreal injection only. Each vial or pre-filled syringe should only be used for the treatment of a single eye. Extraction of multiple doses from a single vial or pre-filled syringe may increase the risk of contamination and subsequent infection. Administration only by qualified physician experienced in administering intravitreal injections. Recommended dose: 2 mg aflibercept (0.05 ml) equivalent to 50 microlitres. For wet AMD, treatment is initiated with 1 injection per month for 3 consecutive doses. The treatment interval is then extended to 2 months. Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly to a minimum of 2 months during the first 12 months of treatment. There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits. Treatment intervals greater than four months between injections have not been studied. For RVO (branch RVO or central RVO), after initial injection, treatment is given monthly. The interval between the 2 doses should not be shorter than 1 month. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). For DME, initiate treatment with 1 injection/month for 5 consecutive doses, followed by 1 injection every 2 months. No requirement for monitoring between injections. After the first 12 months of treatment, and based on visual and/or anatomic outcomes, the treatment interval may be extended such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes; however, there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, treatment should be discontinued. For myopic CNV, a single injection is to be administered. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring should be determined by the treating physician. The interval between 2 doses should not be shorter than 1 month. **Contraindications:** Hypersensitivity to aflibercept or to any of the excipients. Active or suspected ocular or periocular infection. Active severe intraocular inflammation. **Warnings and Precautions:** Intravitreal injections have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Aseptic injection techniques are

essential. Additionally, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Patients must report any symptoms of endophthalmitis or any of the abovementioned events without delay. Increases in intraocular pressure (IOP) were seen within 60 min. of intravitreal injection. Special precaution is needed in poorly controlled glaucoma (no injection while IOP is  $\geq 30$  mmHg). In all cases, IOP and perfusion of optic nerve head must be monitored and managed appropriately. Potential for immunogenicity. Instruct patients to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. Safety and efficacy of concurrent use in both eyes have not been systematically studied. No data is available on the concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular). Risk factors associated with development of retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include large and/or high pigment epithelial retinal detachment. When initiating therapy, use caution in patients with these risk factors for retinal pigment epithelial tears. Withhold treatment in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. Withhold dose and treatment should not be resumed in event of a retinal break until break is adequately repaired. Withhold dose and do not resume treatment earlier than next scheduled treatment in event of: decrease in best-corrected visual acuity of  $\geq 30$  letters compared with last assessment; subretinal haemorrhage involving centre of fovea, or, if size of haemorrhage is  $\geq 50\%$ , of total lesion area. Withhold dose within previous or next 28 days in event of performed or planned intraocular surgery. Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept. Populations with limited data: There is limited experience with treatment of patients with ischaemic CRVO and BRVO. In patients presenting with clinical signs of irreversible ischaemic visual function loss, the treatment is not recommended. There is limited experience in DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when treating such patients. In myopic CNV there is no experience with Eylea in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions. **Undesirable effects:** Very common: Visual acuity reduced, Conjunctival haemorrhage, Eye pain. Common: Retinal pigment epithelial tear (known to be associated with wet AMD; observed in wet AMD studies only), Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia, Ocular hyperaemia. Uncommon: Hypersensitivity (during the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions), Culture positive and culture negative endophthalmitis, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, Anterior chamber flare, Corneal oedema. Rare: Blindness, Cataract traumatic, Vitritis, Hypopyon. **Description of selected adverse reactions:** In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. As with all therapeutic proteins, there is a potential for immunogenicity. **On prescription only.** **Marketing Authorisation Holder:** Bayer AG, 51368 Leverkusen, Germany. **Date of revision of the underlying Prescribing Information:** April 2020.