

Keeping a step ahead of the disease: proactive treatment for nAMD

Emerging evidence: molecular properties and patient outcomes

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Prescribing information for aflibercept solution for injection (Eylea[®], Bayer) can be found on the last page.

Keeping a step ahead of the disease: proactive treatment for nAMD symposium

Chaired by Professor Laurent Kodjikian, University of Lyon, France and President of the French Society of Ophthalmology, a faculty of international retina specialists underscored the suitability of intravitreal aflibercept injection (Eylea®, Bayer) for proactive extended dosing in the management of neovascular age-related macular degeneration (nAMD). Presenters explored evidence from clinical trials and clinical practice supporting the use of a treat-and-extend (T&E) dosing regimen for nAMD starting in the first year of treatment and discussed practical considerations for implementation in clinical practice.

T&E with aflibercept: from design to dosing regimen

Professor Gemmy Cheung, Singapore National Eye Centre, Singapore

The goal of proactive treatment in nAMD is to maximise visual outcomes while reducing treatment burden, Professor Cheung explained. Clinicians internationally and in the United States increasingly prefer to treat patients with active choroidal neovascularisation (CNV) secondary to nAMD using a T&E anti-vascular endothelial growth factor (VEGF) regimen.¹

Aflibercept has a VEGF-A binding affinity up to ~100-fold greater than that of ranibizumab (Lucentis®, Novartis), is the only available anti-VEGF that blocks all VEGF receptor 1 (VEGFR-1) ligands, including VEGF and placental growth factor (PGF), and has a longer intraocular half-life than other intravitreal anti-VEGF agents.²⁻⁶ No conclusions on the durability of aflibercept should be drawn from these preclinical studies.

Clinical study data show that the mean (\pm SD) duration of VEGF-A suppression in the aqueous humor of patients with nAMD following aflibercept injection was 71 ± 18 days (range: 41-109), supporting its use in regimens with extended dosing intervals beyond 8 weeks.⁷ High interpatient variability in duration of VEGF-A suppression, varying up to 16 weeks, further underlines

the need for a proactive flexible regimen tailored to meet individual patient needs, said Professor Cheung.

Sustained vision improvements with proactive extended dosing

Proactive treatment with aflibercept in year 1 provides robust visual acuity (VA) gains that are maintained thereafter with a reduced treatment burden, now supported by rigorous evidence from randomised controlled trials, observed Professor Cheung.⁸⁻¹⁰

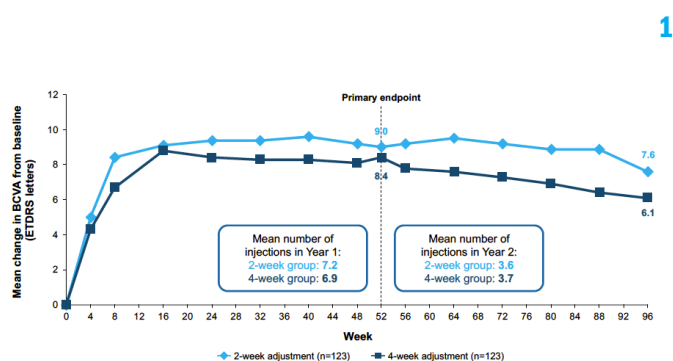
In the pivotal VIEW 1 and VIEW 2 phase 3 studies, approximately half of nAMD patients who received aflibercept every eight weeks (q8w) after 3 initial monthly doses in the first year maintained the best corrected visual acuity (BCVA) gains achieved at week 52 through the second year with injection intervals of 12 weeks.⁸

The PLANET study of aflibercept for patients with polypoidal choroidal vasculopathy (PCV) showed maintenance of functional and anatomical improvements achieved at 52 weeks through 96 weeks using an optional T&E regimen beyond 8-weekly dosing in the second year, with a mean of 4.6 injections in the second

year.^{9,11} At two years, mean BCVA change from baseline was +10.7 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the aflibercept monotherapy group.⁹

Recent findings from the ALTAIR study demonstrated that aflibercept given using a T&E dosing regimen following two different adjustment intervals (2-week and 4-week interval adjustments) achieved sustained VA gains over 96 weeks.¹⁰ Adjustment of T&E treatment intervals was guided by specific anatomic and functional criteria to maintain a stable retina, with a minimum interval of 8 weeks and a maximum of 16 weeks (between weeks 16 to 96).

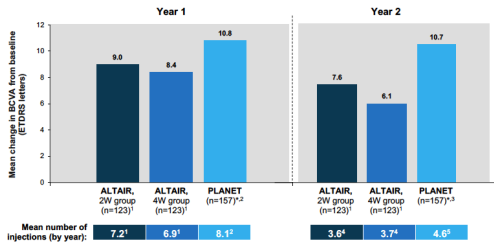
For the primary endpoint of change in BCVA from baseline to week



Full analysis set: last observation carried forward. BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. Source: Adapted from Chj M et al. ALTAIR Investigators. Adv Ther. 2023;37(1):1173-1187.

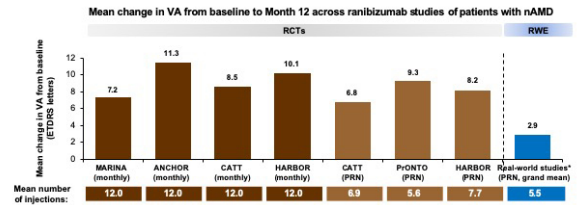
(FIGURE) 1. ALTAIR 96-week results: mean change in BCVA from baseline.

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¹Data from aflibercept + sham rescue PDT arm. In Year 2, patients were eligible to receive optional T&E. T&E was not protocol-mandated and was performed at the discretion of the investigator. 2W, 2-week extension; 4W, 4-week extension; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, pro re nata (as needed); T&E, treat-and-extend. ²Cheng et al. *ALTAIR Investigators. Adv Ther* 2020;35(11):1170-1187. ³Lee WW et al. *JAMA Ophthalmol* 2018; 136 (7): 766-769. ⁴Wong TY et al. *Am J Ophthalmol* 2019; 194: 80-89.

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* Safety outcomes were not reported in this study.

¹Represents average data for the 20 studies included in the review. ²ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration; PRN, pro re nata (as needed); RCT, randomized controlled trial; RWE, real-world evidence; VA, visual acuity. ³Cheng Y. *Eye (Lond)* 2016; 30 (2): 275-286.

(FIGURE) 2. Visual outcomes and treatment exposure over 2 years in clinical trials of proactive aflibercept dosing for nAMD. 3. Meta-analysis of real-world outcomes of ranibizumab PRN for nAMD through 12 months.

52, rapid vision gains were achieved and maintained to week 52: 9.0 letters in the 2-week extension group (n = 124) and 8.4 letters in the 4-week extension group (n = 123), with a mean of 7.2 and 6.9 injections, respectively (FIGURE 1).¹⁰ Improvements in vision at week 52 were largely maintained to week 96 (up to 7.6 letters), achieved with fewer than 4 injections in the second year, with around 30% of patients gaining ≥ 15 letters from baseline at weeks 52 and 96 (FIGURE 2).¹⁰ Rapid reductions in central retinal thickness (CRT) achieved in the first year were maintained to week 96.

The proportion of participants reaching a next intended treatment interval of at least 12 weeks by the end of year 1 was 57%.¹⁰ By week 96, up to 60% of participants were maintained at a treatment interval of 12 weeks or beyond and more than 40% were maintained at an interval of 16 weeks.¹⁰ Up to 96% of patients who reached the maximum possible treatment interval of 16 weeks at the end of year 1 were maintained at that interval to week 96.¹⁰

Topline results from ARIES demonstrate efficacy of proactive T&E aflibercept over 2 years

Results from the ARIES study, presented for the first time at the EURETINA 2019 Congress, corroborate findings supporting the efficacy of proactive T&E dosing with aflibercept for nAMD, noted Professor Cheung.¹²

ARIES is a multinational phase 3b/4 trial that compared the efficacy of aflibercept treatment with an early-start or a late-start T&E regimen in treatment-naïve patients with nAMD treated for 104 weeks. Patients received three initial monthly doses followed by an injection 8 weeks later. At week 16, patients were randomised 1:1 to an early-start T&E arm (2-week interval extension or an initial 4-week interval if dry) or a late-start T&E arm (continued bimonthly aflibercept until week 52, followed by T&E with 2-week interval extension).

Patients recruited to ARIES presented baseline characteristics consistent with typical nAMD.¹³ The early-start T&E regimen (n = 106) was statistically noninferior (-5-letter non-inferiority margin) to the late-start T&E regimen (n = 104) for the primary endpoint of mean BCVA change from week 16 (randomisation) to week 104 (-2.1 versus -0.4 letters, respectively), with one fewer injection (mean of 12.0 vs 13.0 injections).¹² By the end of 2 years, most patients (93% in the early-start group and 96% in the late-start group) maintained vision (< 15 letter loss). By 2 years, approximately one third of patients had a last injection interval of 16 weeks and up to 52% had a last injection interval of 12 weeks or longer.

Professor Cheung concluded that VA gains comparable to those observed with aflibercept in the VIEW studies can be achieved and sustained with proactive T&E dosing, with a majority of patients extended to treatment intervals of 12 weeks or longer by two years.^{8,10,14}

Expanding the evidence: T&E in clinical practice

Dr Peter K Kaiser, Cole Eye Institute, USA

Balancing treatment exposure with patient outcomes is paramount in retinal disease management, emphasised Dr Kaiser.

Real-world effectiveness studies of anti-VEGF therapy for nAMD reveal outcomes from clinical practice that often fail to match those observed in clinical trials of both fixed and pro re nata (PRN, as needed) regimens (FIGURE 3).¹⁵⁻¹⁷

Undertreatment of nAMD with as needed dosing is associated with poor maintenance of vision gains long term, explained Dr Kaiser.^{15,16} A retrospective, observational, open-label effectiveness study of ranibizumab for nAMD (n = 295) given as needed following a loading phase of monthly injections* reported a mean change in VA from baseline (mean 65.0 letters) to year 5 of -9.5 letters (approximate ETDRS letters calculated from

logMAR), with a mean of 14.8 injections administered overall and an average annual treatment frequency of 2.1 to 2.6 injections beyond year 2.¹⁷

Outcomes from clinical trials can be translated to the real world with proactive T&E aflibercept dosing

Dr Kaiser said that treating physicians cannot predict at presentation how many injections individual patients will require to sustain VEGF suppression and maintain stable vision and/or anatomic outcomes.^{18,19}

“Determining appropriate timing and frequency of treatment requires an individual, proactive approach, such as with a T&E dosing regimen,” stressed Dr Kaiser. “Using this strategy, patients are treated at each clinic visit and a decision is taken when retreatment is required to maintain a stable retina.”

Experimental data show that VEGF concentrations in the aqueous humor were suppressed below the lower limit of quantification for about 10 weeks among nAMD patients treated with aflibercept.⁷ In a prospective clinical study of patients with persistent CNV activity under ranibizumab PRN treatment for at least 24 months (n = 7 of the 89 treatment-naïve eyes recruited), aflibercept suppressed VEGF-A in the anterior chamber twice as long as ranibizumab: the mean (SD) duration of suppression was 67 ± 14 days (range: 49-89) for aflibercept and 34 ± 5 days (range: 26-69) for ranibizumab (P < 0.001).²⁰

Real-world outcomes of aflibercept for nAMD are comparable to clinical trial results

Dr Kaiser shared results from real-world studies conducted in different countries and institutions demonstrating that proactive aflibercept dosing can achieve VA results consistent with those observed in randomised clinical trials and superior to reactive as needed anti-VEGF regimens.²¹⁻²⁴

Continuous aflibercept treatment (fixed bimonthly or T&E after initial loading) was associated with significantly greater VA gains than predominantly PRN ranibizumab at month 12 (6.1 vs 1.6 letters, respectively; adjusted difference: +4.1 letters, P < 0.0001) in an EMR study of treatment-naïve nAMD eyes (n = 1,884) from 21 UK hospitals.²¹ Despite a higher mean BCVA at baseline in the aflibercept arm, proactive aflibercept dosed every 8 weeks demonstrated significantly greater VA gains than ranibizumab PRN at month 12 in a retrospective cohort study (n = 1,923) conducted at Moorfields Eye Hospital, London.²²

Among nAMD patients treated in routine clinical practice (n = 108 eyes of 102 patients), good VA gains achieved with fixed dosing aflibercept in year 1 were maintained with proactive T&E dosing to year 3, with a general reduction of injection frequency over 3 years (mean number of injections: 7.4 in year 1, 4.6 in year 2 and 3.9 in year 3).²³ By year 3, close to one third (30.5%) of eyes achieved a 3-line vision gain from baseline and 71% of eyes were dry on optical coherence tomography (OCT).

Another retrospective, observational study of T&E aflibercept outcomes in treatment-naïve nAMD patients (n = 231) in a real-world setting demonstrated long-term VA stability and prevention of VA loss in the majority of patients through 4 years,²⁴ again with a notable reduction in treatment frequency from year 2 onwards. Almost half (46.9%) of patients reached a treatment interval of ≥12 weeks by 2 years.

Why switch to T&E?

Treat-and-extend regimens represent a practical, individualised treatment strategy, aiming to maximise and maintain VA benefit while reducing the frequency of clinic visits.^{19,25} By using a T&E regimen, there is a notable reduction in treatment burden beyond the first year, which translates into a dramatic reduction in clinic visits, emphasised Dr Kaiser. This reduces the need for travel and lowers the caregiver burden.²⁶

Informing nAMD patients of treatment approaches that maintain long-term VA may further increase patient acceptance of a proactive T&E dosing strategy. A preference study among nAMD patients found that T&E was generally more favoured over PRN and fixed bimonthly dosing, primarily because of the high likelihood of long-term VA maintenance and decreasing treatment frequency.²⁷

Dr Kaiser said that a T&E regimen is his preferred approach using intravitreal anti-VEGF therapy for nAMD. “A T&E dosing regimen represents a practical, proactive treatment approach individualised to patient needs. This flexible approach may help reduce the burden of treatment on patients and clinics over time and yet achieve visual outcomes in routine clinic settings that compare well to those observed in clinical trials.”^{21,23,24,28}

**According to the licensed posology of ranibizumab, treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity under continued treatment. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters [Lucentis® 10 mg/ml solution for injection - summary of product characteristics. Dublin, Ireland: Novartis Europharm Limited; 2019. Available at: <https://www.medicines.org.uk/emc/product/307/smpc>]*

The practicalities of T&E in the clinic: panel discussion with Q&A

Moderator: Professor Laurent Kodjikian

Panellists: Professor Gemmy Cheung and Dr Peter K Kaiser

Q. *The patients that we struggle with in clinical practice are those who require continued retreatment at 4-week or 6-week treatment intervals. Should this intensity of treatment exposure be maintained or do you recommend a minimum treatment interval of 8 weeks for such patients?*

A. “The way T&E works is that at the beginning you need to continue with monthly or bimonthly treatment until dry or stable before considering extending the treatment interval. There will always be a small proportion of patients who will require frequent treatment as maintenance therapy. Extension should only be considered when the patient is dry above the retinal pigment epithelium (RPE).

“If patients recur on extended interval dosing, the duration of the treatment interval is shortened, usually by 2-week increments. If patients experience recurrence after shortening to 10-week or 12-week intervals, I usually cut the treatment interval back to around 4 to 6 weeks’ duration and start again.”

—Dr Peter K Kaiser

“Treat-and-extend actually allows you to ensure adequate treatment to those who require retreatment at regular intervals shorter than 8 weeks. Fewer than 10% of participants in the ARIES T&E study were treated more frequently than 8 weekly through 104 weeks.”¹²

—Professor Gemmy Cheung

Q. *What criteria do you recommend for stopping treatment in nAMD or do you continue indefinitely, for example in those who are dry or stable for 3 or more consecutive visits on dosing intervals of 12 weeks or longer?*

A. “There is a high risk of recurrence and significant vision loss after discontinuing anti-VEGF therapy for nAMD patients who have stable or inactive lesions.²⁹ For my patients who have been extended to about 12-week intervals or longer and who can maintain that extension for a year, I offer them the option of continuing T&E dosing or switching to as needed treatment but with frequent regular monitoring visits. And I explain the pros and the cons of both approaches.”

—Dr Peter K Kaiser

Q. *Would you start early with extended dosing or maintain fixed monthly or bimonthly dosing if there is residual or persistent fluid in the inner layer of the retina, for example with intraretinal cysts?*

A. “Subretinal fluid (SRF) is possibly the least harmful compartment of retinal fluid. For example, in the FLUID study, 24-month VA outcomes in patients treated with a relaxed T&E protocol that tolerated some SRF were comparable to those achieved when treatment was intensified to achieve complete resolution of SRF and intraretinal fluid (IRF).³⁰ This is also supported by multiple criteria used to assess disease activity in ALTAIR in addition to fluid status, including VA measurement and signs of new neovascularisation or new macular haemorrhages.”¹⁰

—Professor Gemmy Cheung

Q. *Do you always aim to extend aflibercept for nAMD to 16-week intervals or do you prefer sometimes to maintain a maximum treatment interval of 12 weeks to decrease the risk of recurrence between visits, and how do you decide on the length of extension adjustment?*

A. “Previously, prior to ALTAIR study results, a treatment interval extension of 12 weeks was my maximum. Once results from ALTAIR were presented, I started to extend aflibercept treatment to 16-week intervals in some patients. Extending dosing to 16-week intervals is achievable without any detriment. Personally, I tend to extend gradually by using 2-week adjustments and the outcomes have been good in my clinical practice.”

—Dr Peter K Kaiser

“Extension by 2- or 4-week increments is largely patient dependent. Anecdotally, those who dry early in response to initial anti-VEGF treatment may be extended faster using a 4-week extension. Among patients who require closer scrutiny, a 2-week extension T&E regimen provides a more secure approach. In the FLUID study, the proportion of patients never extended beyond 4-week treatment intervals through month 24 was 13.5% in the intensive group and 2.8% in the relaxed group.³⁰ Overall, approximately one third of participants in the ALTAIR study had a last injection interval of 8 weeks by week 96.”¹⁰

—Professor Gemmy Cheung

SUMMARY OF KEY LEARNINGS

Professor Kodjikian highlighted key symposium learning points:

- Clinical trial data among broad patient populations underline the efficacy of aflibercept T&E for nAMD over 2 years.^{10,12}
- In clinical practice, a proactive T&E regimen with aflibercept starting in year 1 is associated with rapid and sustained vision gains that are maintained with a notably reduced treatment burden through the second year.^{23,24,31}
- In the ALTAIR T&E study of aflibercept for nAMD, up to 60% of patients reached an injection interval of ≥ 12 weeks and more than 40% reached a 16-week injection interval by week 96, with robust VA and anatomic improvements maintained over two years.¹⁰
- The safety profile of aflibercept in the studies discussed was in line with the known safety profile of aflibercept in nAMD.^{10,12}

Emerging evidence: molecular properties and patient outcomes symposium

Chaired by Professor Francine Behar-Cohen, Assistance Publique – Hôpitaux de Paris, France, faculty presenters addressed how emerging insights into drug design and pharmacodynamics may inform patient management and shared perspectives on the role of fluid as the basis for guiding anti-VEGF treatment decisions for retinal disease.

Design, binding and downstream effect

Dr Peter K Kaiser, Cole Eye Institute, USA

Both VEGF-A and PGF contribute to the development of vascular leakage, inflammation and pathological neovascularisation in retinal vascular diseases, Dr Kaiser observed in a presentation reviewing the pathogenesis of retinal disorders (FIGURE 4).³²⁻³⁵

Animal studies demonstrate that PGF inhibition decreases neovascularisation and microvascular abnormalities

VEGF-A acts via VEGFR-1 and VEGFR-2 and plays a critical role in neovascularisation in physiological and pathological conditions.³⁶⁻³⁸ Placental growth factor, a member of the VEGF family of angiogenic factors, binds to VEGFR-1 only^{1,39} and contributes to pathological angiogenic conditions by stimulating endothelial cell activation and migration and recruiting proangio-

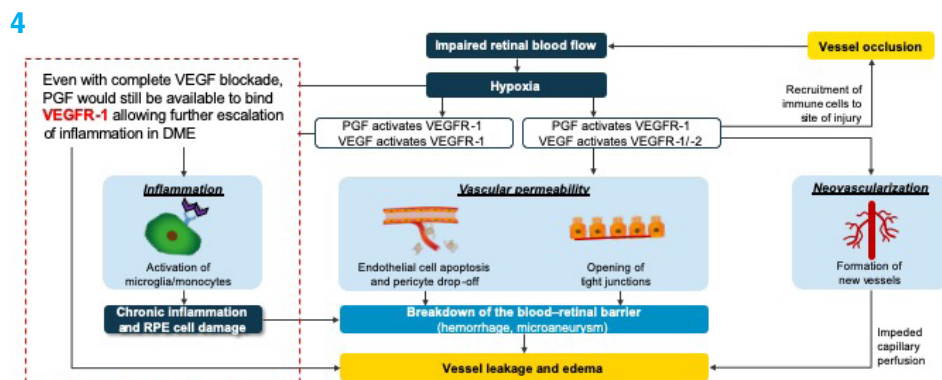
genic cells (myeloid cells, smooth muscle cells and pericytes) to neovascularisation sites.³⁸

Crucially, by binding VEGFR-1, PGF makes VEGF-A available to exert its angiogenic activity through VEGFR-2.³⁸ In animal studies, inhibition of PGF has been shown to decrease neovascularisation and microvascular abnormalities across different disease models.^{38,40}

The design and action of aflibercept allows high-affinity binding to both VEGF and PGF

Aflibercept was specifically designed to provide a multitargeted mechanism of action and strong binding affinity to both VEGF and PGF for durable suppression of intraocular VEGF.^{32,34,35,38,41} Preclinical study data demonstrate that aflibercept has a substantially higher VEGF-A binding affinity than either ranibizumab or unlicensed bevacizumab (FIGURE 5).²

(FIGURE) 4. Schematic diagram illustrating the role of both VEGF and PGF in driving the development of retinal vascular leakage and oedema in diabetic eye disease.

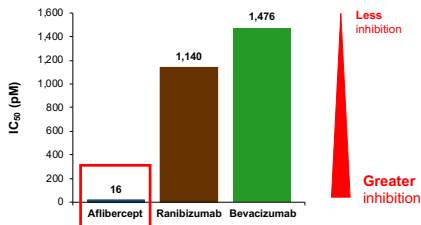


Bevacizumab is not licensed for intravitreal use.

DME, diabetic macular edema; PGF, placental growth factor; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
Whitcup SM et al. *Int J Inflamm* 2013; 2013: 724948. Jousen AM et al. *Mol Vis* 2009; 15: 1418-1428. Danilch A et al. *Prog Retin Eye Res* 2018; 63: 20-68.
Fischer C et al. *Nat Rev Cancer* 2008; 8 (12): 942-956. Aulicino M et al. *J Thromb Haemost* 2003; 1 (7): 1356-1370. Grigsby JG et al. *J Ophthalmol* 2014; 2014: 705783.

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Inhibition of VEGF-A₁₆₅-induced activation* of VEGFR-1 with anti-VEGF agents *in vitro*[‡]



Unlike ranibizumab and bevacizumab, aflibercept also inhibits the activity of PGF[‡]

IC₅₀ of anti-VEGF agents measured *in vitro*, pM

	VEGFR-1 cell line	
	hPGF-2 [†]	
Bevacizumab	NB	
Ranibizumab	NB	
Aflibercept	2,890	

Bevacizumab is not licensed for intravitreal use.

*IC₅₀ at 20 pM. †IC₅₀ at 40 pM. IC₅₀, half maximal inhibitory concentration; ‡Clinical significance is unknown and no conclusions on the durability of aflibercept should be drawn; NB, no detectable blocking under the assay conditions used; PGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Pappadopoulos N *et al*. *Angiogenesis* 2012; 15 (2): 171–185.

(FIGURE) 5. Aflibercept inhibits VEGF induced activation of VEGF receptors more strongly than either ranibizumab or bevacizumab.

Could insights into drug dynamics inform patient management?

Dr Cynthia X Qian, University of Montreal, Canada

“Drug dynamics is an important topic because it provides pharmacological concepts that I believe should shape how we manage and treat our patients,” commented Dr Qian.

Drug concentration and binding affinity are key molecular features that determine how a drug interacts at its target site, Dr Qian explained. The higher VEGF binding affinity of aflibercept compared with ranibizumab may explain, in part, its longer duration of aqueous VEGF suppression.^{2,20}

Should a stable retina guide the T&E regimen in nAMD?

Dr Varun Chaudhary, Hamilton Regional Eye Institute, McMaster University, Canada

Dr Chaudhary argued that, to further optimise T&E dosing strategies for nAMD in clinical practice, there is a need to consider what a stable retina means.

Intraretinal fluid is typically associated with worse VA at baseline and at any time point than SRF or sub-retinal pigment epithelium (sub-RPE) fluid, observed Dr Chaudhary.^{42,43} By contrast, SRF is typically associated with better VA at baseline and superior visual benefit over time than persistent IRF.^{42,43}

What does fluid mean for visual outcomes?

Evidence supports the observation that some retinal fluid can be tolerated without compromising visual outcomes, explained Dr Chaudhary.

Improvement in BCVA from baseline to week 52 was independent of fluid status at week 12 (after the loading phase) in an evaluation of 1,465 nAMD eyes treated with monthly ranibizumab or aflibercept every 8 weeks after 3 initial monthly doses from the VIEW

studies (FIGURE 6).⁴⁴ Among nAMD patients treated with aflibercept in a real-world clinical setting (255 eyes of 223 patients), there was no significant difference in the change in BCVA from baseline between eyes with or without retinal fluid based on OCT status at month 11 ($P = 0.53$).⁴⁵

Residual SRF may not be detrimental to vision and does not appear to be clinically relevant when making treatment decisions in nAMD, suggested Dr Chaudhary. In post hoc analyses of the VIEW studies, despite greater resolution of SRF with aflibercept than with ranibizumab through 52 weeks, improvements in BCVA were similar for both treatments (FIGURE 7),⁴⁶ while eyes with persistent (i.e., residual) IRF at week 24 had significantly worse VA gains than those without (combined treatment groups; $P = 0.0024$).⁴⁷

Dr Chaudhary pointed to consistent evidence that early visual response after treatment initiation is the most relevant predictive factor of treatment success in nAMD.⁴⁸

Visual acuity response after treatment initiation was consistently the most relevant predictive factor for functional outcomes at 1 year in a large OCT dataset from patients receiving monthly or PRN ranibizumab in the HARBOR trial (n = 614).⁴⁸ Horizontal extension of IRF in the foveal region was the most relevant imaging biomarker for BCVA.⁴⁸

The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) study also found that the most important predictor for vision outcome at both year 1 and year 2 was early VA response at month 3.⁴⁹ Through 5 years of follow-up, eyes with non-foveal or foveal IRF (60.8%) had worse VA than eyes without IRF, and eyes with foveal SRF (8.7%) had better VA than eyes without foveal fluid.⁴³

“In our clinical practice, early VA response is what matters most,” emphasised Dr Chaudhary.

Visual outcomes are not necessarily compromised when residual SRF is tolerated

Results from the FLUID study of T&E ranibizumab in nAMD suggest that a zero-tolerance approach to presence of any fluid in the treatment of nAMD may not be necessary (FIGURE 8).³⁰

In the ALTAIR study, aflibercept treatment intervals could be extended or maintained when CRT was stable (i.e., no increase $\geq 100 \mu\text{m}$ compared with the lowest previous value) and based on predefined fluid criteria on OCT (i.e., extend if no fluid, maintain if there is residual but decreased fluid and shorten if new fluid is present). Over 96 weeks, the mean number of injections was 10.4 in both extension groups.¹⁰

“Using a proactive T&E strategy with anti-VEGF therapy in clinical practice is about identifying individual patient response with respect to duration of VEGF suppression,” added Dr Chaudhary. “If fluid is decreased and stable, it is within that effective VEGF suppression window and therefore there is no reason to shorten the interval between injections.”

Personalise the approach to anti-VEGF treatment decision making

While IRF may be associated with unfavourable outcomes,^{43,47} vision may not be compromised if some residual SRF is tolerated using a T&E regimen for nAMD, concluded Dr Chaudhary.

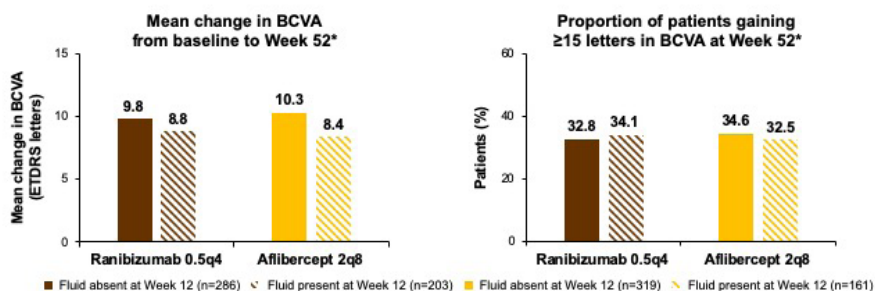
“We are approaching a paradigm shift in terms of defining a stable retina. Imaging biomarkers and VA parameters provide variables that may be useful in identifying an individual patient’s ‘sustained’ VEGF suppression response following treatment,”

Dr Chaudhary added. “A proactive T&E regimen with aflibercept in nAMD may help maintain a stable retina and achieve robust long-term vision gains, without the need for complete resolution of all fluid.”¹⁰

(FIGURE) 6. Post hoc analysis of the VIEW studies examining the impact of fluid status at week 12 and visual outcomes at week 52.

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Post hoc analysis of 1,465 eyes from the VIEW studies examining the impact of fluid status at Week 12 on visual outcomes at Week 52¹



* The most common AEs in this study were conjunctival hemorrhage (21.7%–28.1%) and eye pain (7.0%–10.8%) to Week 52 and conjunctival hemorrhage (23.7%–29.9%) and retinal hemorrhage (13.6%–16.2%) to Week 96²

VIEW was a double-masked, multicenter, parallel-group study assessing non inferiority of aflibercept compared with ranibizumab in the proportion of 2,419 patients maintaining vision at Week 52 (loss of <15 ETDRS letters). Eyes receiving 2mg intravitreal aflibercept every 4 weeks (n=496) are not represented in this graph. 0.5q4, 0.5 mg every 4 weeks; 2q8, 2 mg every 8 weeks, after 3 initial monthly doses; AE, adverse event; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. 1. Khorvaji DM et al. Ophthalmic Surg Lasers Imaging Retina 2016; 47 (3): 238–244. 2. Schmidt-Erfurth U et al. Ophthalmology 2014; 121 (1): 193–201.

How does the evidence inform a proactive approach in clinical practice: panel discussion with Q&A

Moderator: Professor Francine Behar-Cohen

Panellists: Dr Peter K Kaiser, Dr Cynthia X Qian and Dr Varun Chaudhary

Q. Evidence confirms that tolerating some SRF does not damage the retina. Is this changing treatment practice in terms of retreatment decisions?

A. “It has definitely changed my practice. We have good data showing that average intraocular VEGF suppression time varies between anti-VEGF agents. Why are VEGF suppression times important? Because recurrences [of CNV activity] do not happen when VEGF is effectively suppressed.”

— Dr Varun Chaudhary

“Prior to the ALTAIR study, previous T&E paradigms were based on shortening or extending treatment intervals at the time of the next treatment visit. Investigators in ALTAIR utilised a third option as part of the criteria of T&E regimen – reflecting an approach taken by many practitioners in clinical practice – of maintaining the treatment interval if the patient appeared stable. Results from the FLUID study verified that approach in a way. If there is residual but decreased fluid present and no increase in CRT ≥ 100 μm , it means that you can maintain the treatment interval.”

— Dr Peter K Kaiser

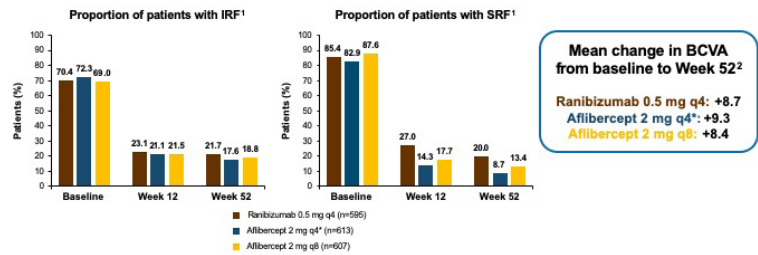
SUMMARY OF KEY LEARNINGS

Professor Behar-Cohen outlined key take-home messages:

- Both VEGF-A and PGF activate VEGF receptors and contribute to vascular leakage, inflammation and pathological neovascularisation in retinal vascular diseases.
- While IRF is associated with poor vision outcomes, evidence suggests that some persistent or residual SRF can be tolerated with proactive treatment without compromising visual outcomes.^{30,43,50}
- A proactive T&E regimen with aflibercept in nAMD may help maintain a stable retina and achieve robust long-term vision gains with extended dosing intervals, without the need for complete resolution of all fluid.

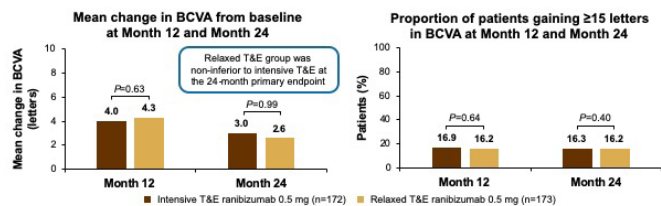
“We should look carefully at OCT scans to distinguish where the fluid is located to guide treatment decisions,” concluded Professor Behar-Cohen.

7



8

Phase IV trial of 349 patients with treatment-naïve nAMD randomized to receive either an ‘intensive’ or a ‘relaxed’ T&E regimen with ranibizumab 0.5 mg based on tolerance to SRF¹



• Ocular AEs were reported in 61.8% of the intensive treatment group (n=173) and 63.8% of the relaxed treatment group (n=174)²

(FIGURE) 7. Post hoc analysis of the VIEW studies comparing fluid response to either aflibercept or ranibizumab, and the association between morphology and VA outcomes, baseline to week 52. 8. FLUID study results at months 12 and 24.

REFERENCES

1. Stone TW, ed. Global Trends in Retina. American Society of Retina Specialists (ASRS); 2017.
2. 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.
3. Carle MV, Chu TG, Tabandeh H, Boyer DS. Intravitreal aflibercept use in the treatment of macular edema from central retinal vein occlusion. *Expert Review of Ophthalmology*. 2013;8(3):227-235.
4. Do DV, Rhoades W, Nguyen QD. Pharmacokinetic study of intravitreal aflibercept in humans with neovascular age-related macular degeneration. *Retina*. 2019 May 27. doi: 10.1097/IAE.0000000000002566. [Epub ahead of print]
5. Krohne TU, Eter N, Holz FG, Meyer CH. Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans. *Am J Ophthalmol*. 2008;146(4):508-12.
6. Krohne TU, Liu Z, Holz FG, Meyer CH. Intraocular pharmacokinetics of ranibizumab following a single intravitreal injection in humans. *Am J Ophthalmol*. 2012;154(4):682-686.
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(3):532-6.
8. Richard G, Monés J, Wolf S, et al. Scheduled versus pro re nata dosing in the VIEW Trials. *Ophthalmology*. 2015;122(12):2497-503.
9. Wong TY, Ogura Y, Lee WK, et al; PLANET Investigators. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy: two-year results of the Aflibercept in Polypoidal Choroidal Vasculopathy Study. *Am J Ophthalmol*. 2019;204:80-89.
10. Ohji M, Takahashi K, Okada AA, et al; ALTAIR Investigators. 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.
11. Lee WK, Iida T, Ogura Y, et al; PLANET Investigators. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(7):786-793.
12. 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.
13. Mitchell P, Souied E, Midena E, et al. Efficacy of intravitreal aflibercept administered using treat and extend regimen over 2 years in patients with neovascular age-related macular degeneration: baseline characteristics of ARIES. Presentation at the 18th European Society of Retina Specialists (EURETINA) Congress; Vienna, Austria, September 20-23, 2018.
14. 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.
15. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol*. 2015;99(2):220-226.
16. Chong V. Ranibizumab for the treatment of wet AMD: a summary of real-world studies. *Eye (Lond)*. 2016;30(2):270-86.
17. Wada I, Oshima Y, Shiose S, et al. Five-year treatment outcomes following intravitreal ranibizumab injections for neovascular age-related macular degeneration in Japanese patients. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(7):1411-1418.
18. Ho AC, Busbee BG, Regillo CD, et al; HARBOR Study Group. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121(11):2181-92.
19. 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;35:1489-1506.

20. 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.
21. Lee AY, Lee CS, Egan CA, et al. UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice. *Br J Ophthalmol*. 2017;101(12):1683-1688.
22. Wagner SK, Fasler K, Afshar F, et al. Ranibizumab and aflibercept: baseline and 12-month visual outcomes of patients at a large tertiary ophthalmic hospital. Presentation at the Association for Research in Vision and Ophthalmology (ARVO) 2018 Annual Meeting; Honolulu, HI, USA, April 29-May 3, 2018.
23. Eleftheriadou M, Gemenetzi M, Lukic M, et al. Three-year outcomes of aflibercept treatment for neovascular age-related macular degeneration: evidence from a clinical setting. *Ophthalmol Ther*. 2018;7(2):361-368.
24. Trainor PG, Pfister IB, Zandi S, et al. Long-term outcome of intravitreal aflibercept treatment for neovascular age-related macular degeneration using a "treat-and-extend" regimen. *Ophthalmol Retina*. 2019;3(5):393-399.
25. 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.
26. Hanemoto T, Hikichi Y, Kikuchi N, et al. The impact of different anti-vascular endothelial growth factor treatment regimens on reducing burden for caregivers and patients with wet age-related macular degeneration in a single-center real-world Japanese setting. *PLoS One*. 2017;12(12):e0189035.
27. Oshima Y, Joko T, Nagai Y, et al. Patient preferences for anti-VEGF treatment regimens for wet age-related macular degeneration in Japan. Presentation at the Association for Research in Vision and Ophthalmology (ARVO) 2019 Annual Meeting; Vancouver, Canada, April 28-May 2, 2019.
28. Barthelmes D, Nguyen V, Daien V, et al; Fight Retinal Blindness Study Group. Two year outcomes of "treat and extend" intravitreal therapy using aflibercept preferentially for neovascular age-related macular degeneration. *Retina*. 2018;38(1):20-28.
29. Vaze A, Fraser-Bell S, Gillies M. Consequences of long-term discontinuation of vascular endothelial growth factor inhibitor therapy in the patients with neovascular age-related macular degeneration. *Acta Ophthalmol*. 2014;92(8):e697-8.
30. 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.
31. Hosokawa M, Morizane Y, Kimura S, et al. Three-year outcomes of a treat and extend regimen of aflibercept for neovascular age-related macular degeneration. Presentation at the Association for Research in Vision and Ophthalmology (ARVO) 2018 Annual Meeting; Honolulu, HI, USA, April 29-May 3, 2018.
32. Autiero M, Luttun A, Tjwa M, Carmeliet P. Placental growth factor and its receptor, vascular endothelial growth factor receptor-1: novel targets for stimulation of ischemic tissue revascularization and inhibition of angiogenic and inflammatory disorders. *J Thromb Haemost*. 2003;1(7):1356-70.
33. Fischer C, Mazzone M, Jonckx B, Carmeliet P. FLT1 and its ligands VEGF and PlGF: drug targets for anti-angiogenic therapy? *Nat Rev Cancer*. 2008;8(12):942-56.
34. Grigsby JG, Cardona SM, Pouw CE, et al. The role of microglia in diabetic retinopathy. *J Ophthalmol*. 2014;2014:705783.
35. Kaur C, Foulds WS, Ling EA. Blood-retinal barrier in hypoxic ischaemic conditions: basic concepts, clinical features and management. *Prog Retin Eye Res*. 2008;27(6):622-47.
36. 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>.
37. Cao Y. Positive and negative modulation of angiogenesis by VEGFR1 ligands. *Sci Signal*. 2009;2(59):re1.
38. Nguyen QD, De Falco S, Behar-Cohen F, et al. Placental growth factor and its potential role in diabetic retinopathy and other ocular neovascular diseases. *Acta Ophthalmol*. 2018;96(1):e1-e9.
39. De Falco S. The discovery of placenta growth factor and its biological activity. *Exp Mol Med*. 2012;44(1):1-9.
40. Huang H, He J, Johnson D, et al. Deletion of placental growth factor prevents diabetic retinopathy and is associated with Akt activation and HIF1 α -VEGF pathway inhibition. *Diabetes*. 2015;64(1):200-12.
41. Miyamoto N, de Kozak Y, Jeanny JC, et al. Placental growth factor-1 and epithelial haemato-retinal barrier breakdown: potential implication in the pathogenesis of diabetic retinopathy. *Diabetologia*. 2007;50(2):461-70.
42. Schmidt-Erfurth U, Waldstein SM. A paradigm shift in imaging biomarkers in neovascular age-related macular degeneration. *Prog Retin Eye Res*. 2016;50:1-24.
43. Jaffe GJ, Ying GS, Toth CA, et al; Comparison of Age-related Macular Degeneration Treatments Trials Research Group. Macular morphology and visual acuity in year five of the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology*. 2019;126(2):252-260.
44. Moshfeghi DM, Hariprasad SM, Marx JL, et al. Effect of fluid status at week 12 on visual and anatomic outcomes at week 52 in the VIEW 1 and 2 trials. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(3):238-44.
45. Almuhtaseb H, Kanavati S, Rufai SR, Lotery AJ. One-year real-world outcomes in patients receiving fixed-dosing aflibercept for neovascular age-related macular degeneration. *Eye (Lond)*. 2017;31(6):878-883.
46. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. *Ophthalmology*. 2016;123(7):1521-9.
47. Eichenbaum D. Association between early vision-related quality of life outcomes and anatomic dryness response in neovascular age-related macular degeneration (nAMD): a post-hoc analysis of VIEW trials. Presentation at the Association for Research in Vision and Ophthalmology (ARVO) 2019 Annual Meeting; Vancouver, Canada, April 28-May 2, 2019.
48. Schmidt-Erfurth U, Bogunovic H, Sadeghipour A, et al. Machine learning to analyze the prognostic value of current imaging biomarkers in neovascular age-related macular degeneration. *Ophthalmol Retina*. 2018;2(1):24-30.
49. Ying GS, Maguire MG, Daniel E, et al; Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group. Association of baseline characteristics and early vision response with 2-year vision outcomes in the Comparison of AMD Treatments Trials (CATT). *Ophthalmology*. 2015;122(12):2523-31.
50. Singer M. Presentation at the 42nd Annual Macula Society Meeting; Bonita Springs, FL, USA, February 13-16, 2019.

Eylea® 40 mg/ml solution for injection in a vial (afibercept) Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. Indication(s): Treatment of neovascular (wet) age-related macular degeneration (wAMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DMO) in adults and visual impairment due to myopic choroidal neovascularisation (myopic CNV). **Posology & method of administration:** For intravitreal injection only. Must be administered according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. Each vial should only be used for the treatment of a single eye. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection. The vial contains more than the recommended dose of 2 mg. The extractable volume of the vial (100 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Refer to SmPC for full details. **Adults:** The recommended dose is 2 mg aflibercept, equivalent to 50 microlitres. For wAMD 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 4 months between injections have not been studied. For RVO (branch RVO or central RVO), after the initial injection, treatment is given monthly at intervals not shorter than 1 month. Discontinue if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. Treat monthly until maximum visual acuity and/or 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. Shorten treatment intervals if visual and/or anatomic outcomes deteriorate. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response. For DMO, 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. **Hepatic and/or renal impairment:** No specific studies have been conducted. Available data do not suggest a need for a dose adjustment. **Elderly population:** No special considerations are needed. Limited experience in those with DMO over 75 years old. **Paediatric population:** No data available. **Contraindications:** Hypersensitivity to active substance or any excipient; active or suspected ocular or periorbital infection; active severe intraocular inflammation. **Warnings & precautions:** As with other intravitreal therapies endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract have been reported. Aseptic injection technique is essential. 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 above mentioned events without delay. Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection; special precaution is needed in patients with poorly controlled glaucoma (do not inject while the intraocular pressure is ≥ 30 mmHg). Immediately after injection, monitor intraocular pressure and perfusion of optic nerve head and manage appropriately. There is a potential for immunogenicity as with other therapeutic proteins; patients should report any signs or symptoms of intraocular inflammation e.g pain, photophobia or redness, which may be a clinical sign of hypersensitivity. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal

injection of vascular endothelial growth factor (VEGF) inhibitors. Safety and efficacy of concurrent use in both eyes have not been systemically studied. No data is available on concomitant use of Eylea with other anti-VEGF medicinal products (systemic or ocular). Caution in patients with risk factors for development of retinal pigment epithelial tears including large and/or high pigment epithelial retinal detachment. Withhold treatment in patients with: rhegmatogenous retinal detachment or stage 3 or 4 macular holes; with retinal break and do not resume treatment until the break is adequately repaired. Withhold treatment and do not resume before next scheduled treatment if there is: decrease in best-corrected visual acuity of ≥ 30 letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage $\geq 50\%$ of total lesion area. Do not treat in the 28 days prior to or following 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 child-bearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection. In patients presenting with clinical signs of irreversible ischaemic visual function loss, aflibercept treatment is not recommended. Populations with limited data: There is limited experience in DMO 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. **Interactions:** No available data. **Fertility, pregnancy & lactation:** Not recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-foetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding. Excretion in human milk: unknown. Male and female fertility impairment seen in animal studies with high systemic exposure not expected after ocular administration with very low systemic exposure. **Effects on ability to drive and use machines:** Possible temporary visual disturbances. Patients should not drive or use machines if vision inadequate. **Undesirable effects:** Very common: Visual acuity reduced, conjunctival haemorrhage (wAMD phase III studies: increased incidence in patients receiving anti-thrombotic agents), eye pain. Common: retinal pigment epithelial tear (known to be associated with wAMD; observed in wAMD studies only), detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or ocular hyperaemia. Serious: cf. CI/W&P - in addition: blindness, culture positive and culture negative endophthalmitis, cataract traumatic, transient increased intraocular pressure, vitreous detachment, retinal detachment or tear, hypersensitivity (during the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions), vitreous haemorrhage, cortical cataract, lenticular opacities, corneal epithelium defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare, 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. Consult the SmPC in relation to other side effects. **Overdose:** Monitor intraocular pressure and treat if required. **Incompatibilities:** Do not mix with other medicinal products. **Special Precautions for Storage:** Store in a refrigerator (2°C to 8°C). Do not freeze. Unopened vials may be stored at room temperature (below 25°C) for up to 24 hours before use. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** Single vial pack £816.00. MA Number(s): EU/1/12/797/002. **Further information available from:** Bayer plc, 400 South Oak Way, Reading RG2 6AD, United Kingdom. Telephone: 0118 206 3000. **Date of preparation:** July 2018.

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