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SUPPLEMENT

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TEN YEARS OF INNOVATION in the treatment of exudative retinal disease

EURETINA 2022 Congress Bayer Symposia Highlights

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This publication, produced on behalf of Bayer Consumer Care AG, highlights satellite symposia organized and funded by Bayer and presented during the European Society of Retina Specialists (EURETINA) 2022 Congress, held in Hamburg, Germany, September 1–4, 2022. The views of faculty speakers do not necessarily reflect the opinion of Bayer. Medical writing support was provided by Rod McNeil Associates and was funded by Bayer.

Prescribing information for aflibercept solution for injection (EYLEA®, Bayer AG) in the European Union can be found on the last page.

Cover image courtesy of IAN TREHERNE (eye condition: Retinitis pigmentosa type 2) via the EYE-SIGHT project

Benefits beyond vision:
Ten years of delivering outcomes that matter

Symposium Chair: Professor Andreas Stahl, University Medicine Greifswald, Germany

Symposium faculty reviewed long-term efficacy outcomes of aflibercept 2mg (EYLEA®, Bayer AG), first launched a decade ago, across real-world patient populations with exudative retinal disease, considered an evolving treatment landscape and highlighted emerging monitoring technologies and cell and gene therapies.

A decade-long legacy: From clinical trials to the real world

Presenter: Professor Focke Ziemssen, Leipzig University, Germany

Professor Ziemssen discussed key learnings from the last decade in the management of exudative retinal disease that he said have helped optimize anti-vascular endothelial growth factor (VEGF) outcomes and reduce treatment burden for patients, carers and clinics.

Vascular endothelial growth factor inhibitor ranibizumab (Lucentis, Novartis) was approved by European Medicines Agency (EMA) for the treatment of neovascular age-related macular degeneration (nAMD) in 2007, following landmark clinical trials showing that treatment not only reduced vision loss but also improved visual acuity (VA).[1] First experience with ranibizumab therapy showed that, despite good vision outcomes with fixed monthly dosing in clinical trials, as needed (pro re nata [PRN]) dosing was associated with undertreatment and suboptimal vision outcomes in clinical practice.[2,3]

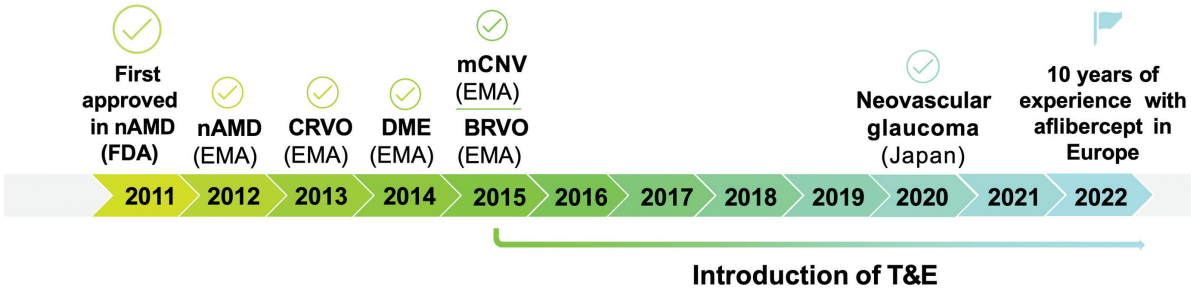
Aflibercept was approved by EMA in 2012, pioneering a multitargeted approach by blocking the ligands that activate two receptor tyrosine kinases, vascular endothelial growth factor receptors 1 and 2 (VEGFR-1 and VEGFR-2) (**FIGURE 1**). Aflibercept blocks and inhibits all VEGFR-1 ligands, including placental growth factor (PIGF), VEGF-A and VEGF-B, and the key VEGFR-2 ligand, VEGF-A.[4–7]

Across indications in nAMD, diabetic macular edema (DME) and retinal vein occlusion (RVO), randomized clinical trials of aflibercept 2mg demonstrated long-term maintenance of meaningful vision gains, helping to provide patients with independence and improved quality of life.[8,9] For example, in the landmark VIEW nAMD clinical trials of bimonthly aflibercept after initial monthly dosing, meaningful vision gains were observed through week 96, which were maintained long-term through two further years of follow-up in the VIEW 1 extension study.[10,11] Injection intervals up to every 12 weeks (q12w) were permitted in the extension study, achieved by 48% of patients.[11]

Meaningful vision gains achieved in real-world practice similar to clinical trials

Real-world evidence from non-interventional studies confirms the long-term effectiveness and safety of aflibercept in exudative retinal disease, added Professor Ziemssen.[12] Following its introduction, reported outcomes from routine clinical practice in Germany, UK and France demonstrated that aflibercept treatment (bimonthly after 3 initial monthly doses) in treatment-naïve patients with nAMD achieved sustained vision gains at one year that were similar to those observed in pivotal clinical trials (aver-

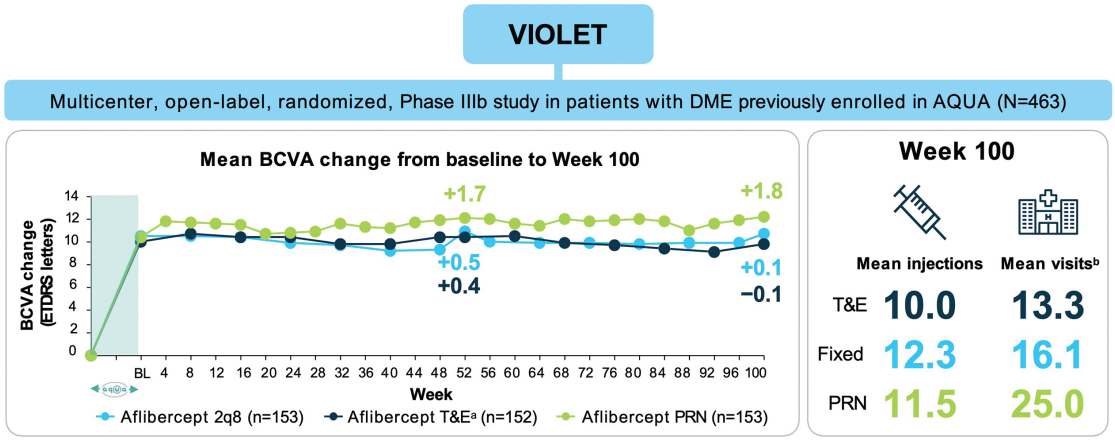
Figure 1. Aflibercept 2mg: a decade of innovation.



Aflibercept is approved for the treatment of neovascular glaucoma in Japan only. BRVO, branch retinal vein occlusion. CRVO, central retinal vein occlusion. DME, diabetic macular edema. EMA, European Medicines Agency. FDA, Food and Drug Administration. mCNV, myopic choroidal neovascularization. nAMD, neovascular age-related macular degeneration. T&E, treat-and-extend.

Figure 2. VIOLET study of DME patients: long term vision gains with extended treatment intervals.

nAMD DME RVO



The use of aflibercept in this study is not in accordance with the licensed posology for aflibercept in DME. 2q8, 2mg every 8 weeks. BCVA, best corrected visual acuity. BL, baseline. DME, diabetic macular edema. ETDRS, Early Treatment Diabetic Retinopathy Study. PRN, *pro re nata* (as needed). T&E, treat-and-extend. [a]The minimum treatment interval was 8 weeks, with no upper limit for maximum treatment interval. Treatment intervals were adjusted, typically in 2-week increments, based on visual and anatomic measures. [b]Includes screening visit, Week 52 visit and Week 100 visit in VIOLET. Adapted from: Garweg JG, *et al. Adv Ther* 2022;39:2701–2716.

age VA gain of +6.8 to +8.0 Early Treatment Diabetic Retinopathy Study [ETDRS] letters compared to a mean VA improvement of +8.4 letters in the VIEW studies).[10,13–16]

Proactive T&E may reduce unnecessary treatment burden

Professor Ziemssen explained that subsequent approval of a treat-and-extend (T&E) regimen for aflibercept underscored the benefits of personalizing treatment to individual patient needs. "We learnt that proactive extended dosing using a T&E approach helps to maintain vision gains while avoiding the risk of over- and under-treatment, reducing unnecessary treatment burden."[8]

Clinical trial data evaluating aflibercept T&E demonstrate maintenance of long-term vision gains with proactive individualized dosing up to every 16 weeks (q16w) in nAMD.[17] The phase 4 ALTAIR study of aflibercept T&E in treatment-naïve patients with nAMD (n=247) reported a mean change in best-corrected visual acuity (BCVA) from baseline to week 96 of +6.1 to +7.6 letters, with 46.3% of patients in the T&E 4-week adjustment arm achieving a last injection interval of 16 weeks and up to 60.2% of patients achieving a last injection interval of ≥12 week at final study visit.[17]

In the phase 3b VIOLET study (n=463) of aflibercept in DME, vision gains were maintained long-term over 100 weeks beyond the first year of treatment; moreover, flexible aflibercept T&E was non-inferior to PRN or fixed dosing regimens for change in BCVA from baseline, with fewer injections and clinic visits overall compared with either PRN or fixed regimens. (**FIGURE 2**).[18] The updated licensed posology for aflibercept 2mg in DME allows individualized T&E dosing during the first year of therapy.[4]

Wealth of real-world evidence supports proactive extended dosing with aflibercept

Real-world evidence supports the benefits of individualizing treatment using a T&E approach, with reported vision gains comparable to clinical trials, observed Professor Ziemssen.[19–23]

Among patients with nAMD treated with aflibercept T&E in real-life settings, vison gains were maintained through year 4, with a reduction in treatment burden after the first year.[19–21] The APOLLON study of aflibercept in patients with DME in routine clinical practice in France showed bimonthly treatment after initial monthly dosing was associated with improvements in functional and anatomic outcomes in both treatment-naïve and previously treated patients.[22] Among newly diagnosed patients with macular edema secondary to central RVO, Eleftheriadou et al. reported a mean (±SD) vision gain of 15.1 ± 20.2 letters with 50% of patients gaining ≥15 letters at 52 weeks' follow-up using an individualized aflibercept T&E protocol after initial loading.[23]

Well-established safety profile, gained from extensive clinical experience

Aflibercept's efficacy and safety profile has been established across multiple pivotal randomized clinical trials and is supported by over a decade of pharmacovigilance monitoring and real-world evidence, noted Professor Ziemssen. Since launch, there are over 8 million patient-years of aflibercept exposure worldwide.[24] Incidence rates of select adverse events including intraocular inflammation (1.0 in 10,000 units sold) and endophthalmitis (0.6 in 10,000 units sold) are low.[25]

Professor Ziemssen concluded: "In summary, first pioneered a decade ago, aflibercept has set a high bar for efficacy, durability and safety across retinal disease and continues to drive improvements in real-world clinical practice."

Aflibercept: Behind the molecule

Presenter: Professor Richard Gale, York Teaching Hospitals NHS Foundation Trust, UK

The role of VEGFR-1 and VEGFR-2 in the pathogenesis of exudative retinal disease

Excessive activation of VEGFR-1 and VEGFR-2 by ligands VEGF-A and PIGF activates inflammation, neovascularization and retinal vascular leakage and edema, three underlying pathways in the pathogenesis of retinal vascular disease, explained Professor Gale (**FIGURE 3**).

The VEGF-A signaling pathway is considered the master regulator of pathological angiogenesis.[26] VEGF-A binds VEGFR-1 and VEGFR-2, whereas VEGF-B and PIGF only bind VEGFR-1. Excessive VEGFR-1 activation can affect vascular permeability and induce macrophage and microglia production of proinflammatory and proangiogenic mediators.[6] Both VEGF and PIGF levels are significantly elevated in patients with retinal vascular disease compared with controls.[27–30]

Multitargeted action to address relevant pathways in disease pathogenesis

Aflibercept is a multitargeted fusion protein incorporating domains from two VEGF receptors for tight binding of VEGF-A and PIGF, observed Professor Gale.[4,5,7,26] Aflibercept binding of VEGF-A creates what has been described as a "nearly irreversible two-fisted grasp", which inhibits downstream effects of VEGFR-1 and VEGFR-2 activation.[5,31]

Aflibercept also binds the additional VEGF family ligands VEGF-B and PIGF.[5] Placental growth factor in particular can synergize with VEGF-A to promote abnormal angiogenesis, vascular leakage and inflammation.[4-6] A prospective cohort study showed significantly decreased intraocular VEGF and PIGF concentrations from baseline to month 2 in treatment-naïve patients with DME following short-term aflibercept therapy (**FIGURE 4**).[32]

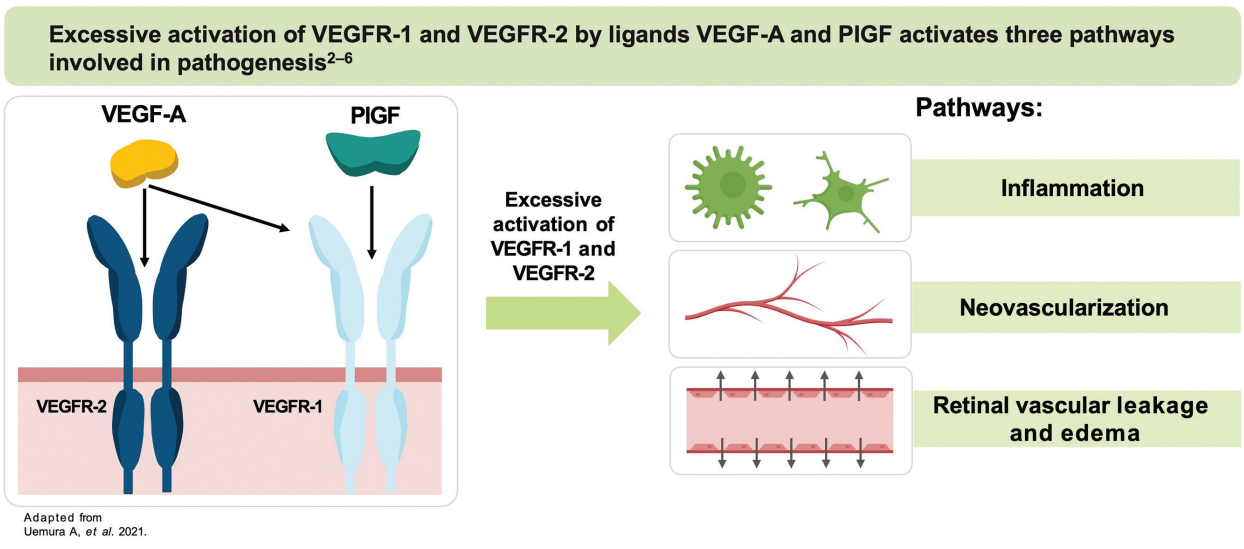
Molecular properties of available intravitreal anti-VEGF agents differ

The treatment landscape of approved intravitreal anti-VEGF inhibitors continues to expand. Brolucizumab (Beovu, Novartis), a single-chain antibody fragment, was first approved in 2019 and faricimab (Vabysmo, Roche), a bispecific antibody, was approved in 2022. Faricimab selectively binds to VEGF-A and angiopoietin-2 (Ang-2). The VEGF antigen binding fragment of faricimab is identical to ranibizumab.[33]

Available data for individual studies evaluating anti-VEGF agents separately suggest that aflibercept has a higher VEGF binding affinity and longer estimated half-life than ranibizumab, brolucizumab and faricimab.[5,34–40] Aflibercept binds to $VEGF_{165}$ with a binding affinity ~100-fold greater than ranibizumab, while the binding affinity of faricimab for human VEGF-A is similar to ranibizumab.[5,35] It was emphasized that these data are from different studies reporting the binding affinity of different anti-VEGF agents and the data are not necessarily directly comparable.

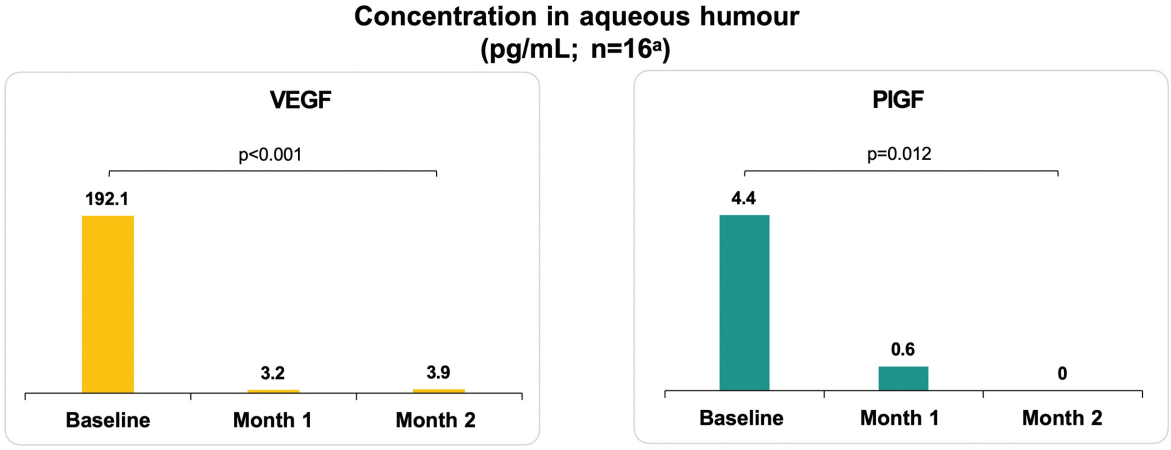
Among VEGF family ligands, ranibizumab, brolucizumab and faricimab specifically target only VEGF-A, and therefore proangiogenic effects mediated by PIGF could still be activated through VEGFR-1 signaling.[5,6,41,42] Aflibercept is the only widely approved intravitreal anti-VEGF agent that blocks all VEGFR-1 ligands, including PIGF, and the key VEGFR-2 ligand, VEGF-A, Professor Gale observed.[6,43,44]

Figure 3. VEGFR-1 and VEGFR-2 play a critical role in angiogenesis.[1]



Visuals are for illustration purposes only.
PIGF, placental growth factor. VEGF, vascular endothelial growth factor. VEGFR, vascular endothelial growth factor receptor. **1.** De Falco S. *Exp Mol Med* 2012;44:1–9. **2.** EYLEA® (aflibercept solution for injection) Summary of Product Characteristics. Berlin, Germany: Bayer Pharma AG. **3.** Cao Y. *Sci Signal* 2009;2:re1. **4.** Uemura A, *et al. Prog Retin Eye Res* 2021;84:100954. **5.** Papadopoulos N, *et al. Angiogenesis* 2012;15:171–185. **6.** National Cancer Institute. Angiogenesis inhibitors. Available at: https://www.cancer.gov/about- cancer/treatment/types/immunotherapy/angiogenesis-inhibitors-fact-sheet. Accessed: August 2022.

Figure 4. Study results showing aflibercept significantly decreased intraocular VEGF and PlGF levels from baseline to month 2 in patients with DME.



Molecular structures are visuals for illustration purposes only. DME, diabetic macular edema. PlGF, placental growth factor. VEGF, vascular endothelial growth factor. [a]Prospective cohort study of treatment-naïve patients with DME. 17 patients enrolled; 16 patients completed the study. Patients received monthly aflibercept 2mg for three months (baseline, Month 1 and Month 2). Aqueous samples for cytokine analysis were obtained immediately before each aflibercept 2mg injection (baseline, Month 1, Month 2) and cytokines concentrations were measured using multiplex immunoassay.
Adapted from: Juncal VR, *et al. J Ocul Pharmacol Ther* 2020;36:697–702.

A vision for the future: What does the next 10 years hold?

Presenter: Professor Nicole Eter, University of Münster, Germany

Novel anti-VEGF formulations

Previous evaluations targeting novel pathways including platelet-derived growth factor receptor (PDGFR) and dual inhibition of Ang-2 and VEGF showed no added clinical benefits over current anti-VEGF therapy in patients with nAMD or DME.[45–47]

Phase 3 TENAYA and LUCERNE trials of VEGF-A/Ang-2 inhibitor faricimab in patients with nAMD showed noninferiority to aflibercept for BCVA change from baseline at week 48.[48] Across both trials, more than three quarters of faricimab patients achieved quarterly or longer dosing during the first year. Patients randomized to aflibercept received fixed bimonthly treatment after an initial loading phase, with no treatment extension permitted.

The US Food and Drug Administration (FDA) drug approval package for faricimab provides further insights regarding the outcomes reported in TENAYA and LUCERNE.[49] Regarding extended faricimab dosing up to q16w, the FDA review comments note: "The studies simply showed that some patients are very responsive to anti-VEGF therapies and may be dosed less frequently which is already known from clinical practice." Moreover, the contribution of Ang-2 inhibition to the treatment effect and clinical response for nAMD and DME has yet to be established.[49]

Professor Eter commented that targeting VEGF and PlGF may offer potential to improve treatment outcomes. For example, increasing the initial molar dose of an anti-VEGF agent may provide a longer duration of VEGF suppression and provide added benefits to patients with a decreased treatment burden.

Exploring the potential of cell and gene therapies

Considering future developments, at-home monitoring applications may provide meaningful benefits to patients with exudative retinal disease, for example by increasing early detection of nAMD with good vision and for virtual monitoring of treatment response using home optical coherence tomography (OCT).[50–52]

Professor Eter concluded by noting that cell and gene therapies show promising potential in the treatment of degenerative retinal diseases.[53–55] Early-phase cell therapy trials for the treatment of retinal degeneration are investigating retinal progenitor cell-based transplantation, embryonic stem cells, induced pluripotent stem cells (iPSCs) and mesenchymal stromal cells.[53] Several different retinal gene therapies and novel delivery routes are currently being evaluated in clinical trials.[55,56] Bayer is exploring cell and gene therapy options for retinal therapeutics.

HIGHLIGHTS

Symposium Chair: Professor Andreas Stahl

- Aflibercept, a recombinant VEGF receptor fusion protein with a multitargeted action, blocks and inhibits all VEGFR-1 ligands, including PlGF and VEGF-B, and the key VEGFR-2 ligand, VEGF-A.[6,7]
- The introduction of aflibercept has helped transform the approach to clinic management and patient outcomes across exudative retinal disease, enabling long-term preservation of vision with reduced treatment burden using proactive extended dosing.[17,57–59]

Durability across indications:
Seeing from the patient's perspective

Symposium Chairs: Professor Gemmy Cheung, Singapore National Eye Centre, Singapore and Professor Varun Chaudhary, McMaster University, Canada

Symposium faculty presented patient case reports across indications in exudative retinal disease, exploring the application of a proactive individualized T&E regimen with aflibercept 2mg and importance of early treatment to secure long-term maintenance of disease control and optimal vision outcomes.

Exploring patient cases in nAMD

Presenter: Professor Varun Chaudhary

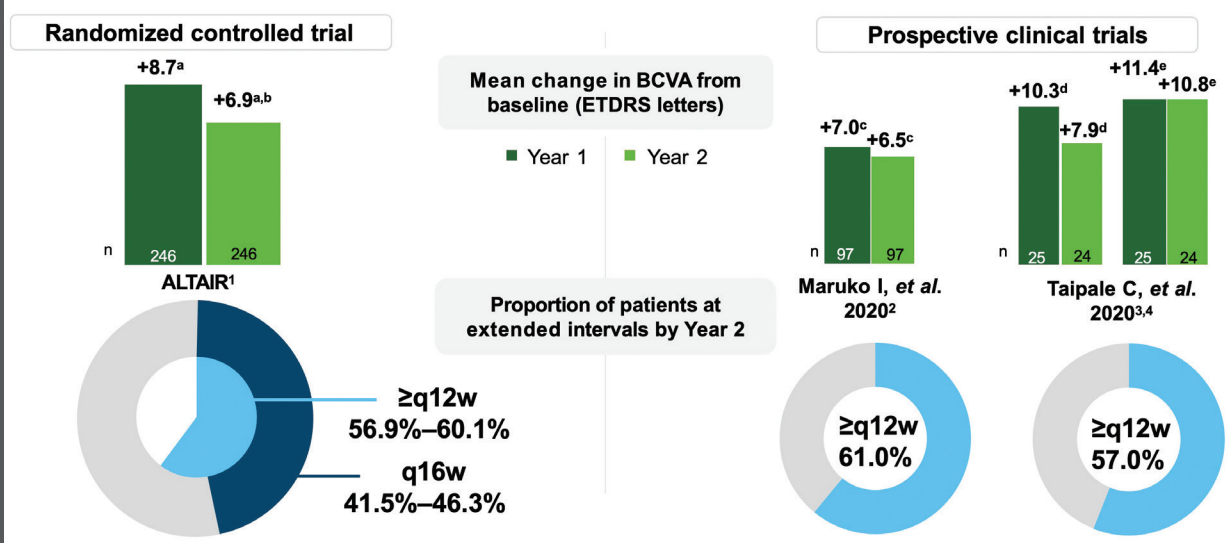
Professor Chaudhary explained that AMD is one of leading causes of vision loss globally in adults over 50 years of age and that nAMD is responsible for approximately 90% of blindness cases caused by AMD.[60,61]

The ALTAIR study as well as other pragmatic clinical trials have demonstrated maintenance of vision gains with extended aflibercept dosing up to q16w through 2 years in patients with nAMD (**FIGURE 5**).[17,62,63] Real-world evidence in nAMD shows that vision gains can be maintained through year 4 and beyond with proactive aflibercept T&E, with a notable reduction in treatment burden after the first year.[19–21]

"The T&E protocol utilized in ALTAIR is straightforward to implement in routine clinical practice, with response assessed based on vision, fluid status and presence or absence of new hemorrhage," commented Professor Chaudhary.

The first case presentation described a male patient with acute vision loss in his right eye. Baseline BCVA was 50 letters (20/100) and OCT retinal thickness was 327.5 µm. Examination revealed nAMD in the right eye and dry AMD in the fellow eye. Intraretinal fluid and hyperreflective material were identified on OCT.

Figure 5. Aflibercept T&E in nAMD.



Please note that this information is from separate, independent studies and therefore should be interpreted carefully; no direct comparisons should be made. In ALTAIR, differences between treatment arms are not confirmatory. BCVA, best corrected visual acuity. ETDRS, Early Treatment Diabetic Retinopathy Study. logMAR, logarithm of the minimum angle of resolution. nAMD, neovascular age-related macular degeneration. q12w, every 12 weeks. q16w, every 16 weeks. T&E, treat-and-extend. [a]Pooled from 2-week T&E and 4-week T&E treatment arms. [b]At Week 96. [c]Approximate ETDRS conversion from logMAR. [d]Treatment intervals were extended by 1 week at a time up to 12 weeks, and then by a further 2 weeks at a time up to 16 weeks. [e]Treatment intervals were first extended to 8 weeks, and then by 2 weeks at a time up to 16 weeks. **1.** Ohji M, *et al. Adv Ther* 2020;37:1173–1187. **2.** Maruko I, *et al. Ophthalmol Retina* 2020;4:767–776. **3.** Taipale C, *et al. Acta Ophthalmol* 2020;98:267–273. **4.** Taipale C, *et al. Adv Ther* 2020;37:2256–2266.

* The clinical case presentations are from the clinical practice of the speaker or as otherwise stated. The case reports are examples of single patient cases and are not representative for the outcomes of other patients. Individual outcomes differ and may not always reflect the averaged outcomes for all patients. Treatment decisions should be taken based on the individual patient and the local product information.

Treatment was initiated with 3 monthly aflibercept injections to resolve fluid and maximize vision early on. At month 4, BCVA was 80 letters (20/25) and retinal fluid had completely resolved. In this case, the patient was treated with aflibercept T&E using 2-week interval adjustments, with no fluid recurrence and continued VA improvement at month 6. Clearly stable, the treatment interval was extended to 12 weeks. Atrophic cysts in the nuclear layer were observed but vision remained stable. Following a further injection at 12 weeks, treatment was extended to q16w during the second year. This patient showed a good early response to monthly aflibercept treatment and was maintained effectively with extended dosing up to q16w through 2 years.

The second case report described an 81-year-old female patient presenting with a history of decreased vision in the right eye. Fluorescein angiography revealed hyperfluorescence and leakage suggestive of a neovascular membrane; OCT confirmed a large pigment epithelial detachment (PED) and subretinal fluid (SRF). After an initial loading phase with ranibizumab, monthly retreatment was continued due to active disease. The patient was in residential care and found it difficult to sustain monthly appointments, expressing a wish to discontinue treatment. Following a treatment switch to aflibercept, visual and anatomic outcomes improved. At 18 months on aflibercept q12w, BCVA was 20/60 and CST was 229 µm. The patient could not return for 16 weeks due to illness. Outcomes remained stable on extended q16w dosing intervals and the patient continued to do well through 8 years of aflibercept treatment at regular 4-monthly intervals.

In summary, Professor Chaudhary said proactive aflibercept T&E up to q16w as early as the first year enables patients with nAMD to achieve and maintain meaningful long-term vision gains while minimizing treatment and clinic burden.[11,17,64,65]

Exploring patient cases in DME

Presenter: Professor Justus G. Garweg, Berner Augenklinik, University of Bern, Switzerland

An estimated ~27 million adults are affected by DME worldwide, with the majority experiencing life-changing visual impairment.[66–70] Patients with DME are typically of working age and approximately two-thirds present with VA below 69 letters.[66–69]

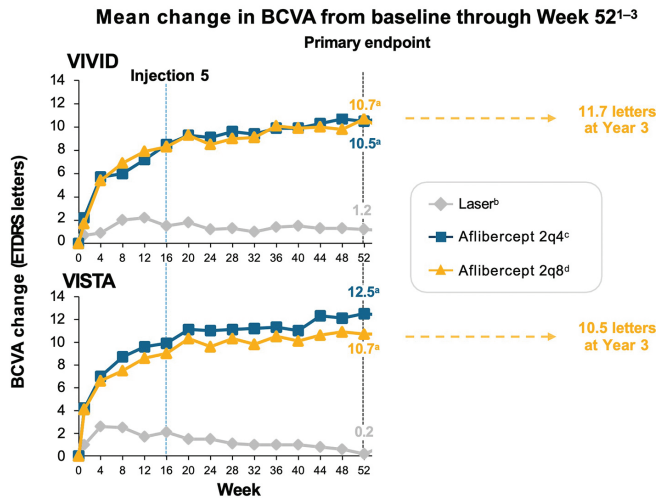
Early, intensive dosing is key to maintaining long-term vision gains in patients with DME, emphasized Professor Garweg.[71] In the phase 3 VIVID and VISTA trials of aflibercept for DME, vision gains from baseline continued through five initial monthly doses and were maintained over 148 weeks with bimonthly dosing (**FIGURE 6**).[57,71,72]

Evidence further supports individualized treatment following

Figure 6. VIVID and VISTA trials demonstrate that early, intensive dosing with aflibercept is key to maintaining long-term vision gains.

VIVID and VISTA:
two similarly designed, double-masked, randomized, Phase III trials in treatment-naïve patients with DME (N=872)

Vision gains continued through **five initial monthly doses** in Year 1 and were maintained over 148 weeks[1] (aflibercept 2q8 arm)

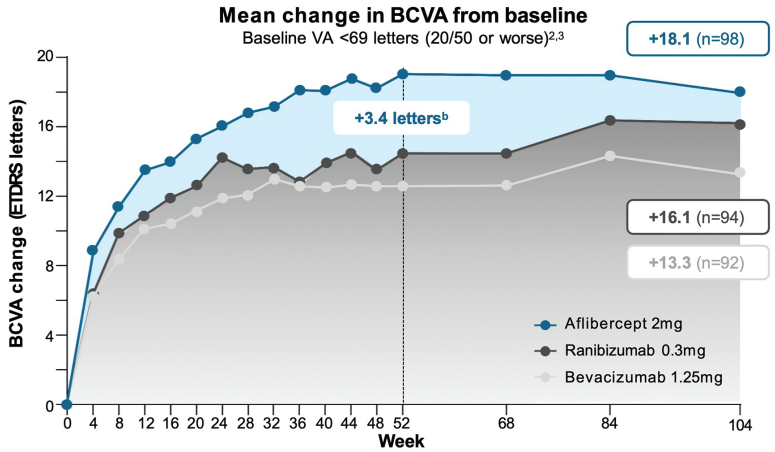


The use of aflibercept in the 2q4 study arm in VIVID and VISTA was not in accordance with the licensed posology for aflibercept in DME. 2q4, 2mg every 4 weeks. 2q8, 2mg every 8 weeks, after five initial monthly doses. BCVA, best corrected visual acuity. DME, diabetic macular edema. ETDRS, Early Treatment Diabetic Retinopathy Study. LOCF, last observation carried forward. OCT, optical coherence tomography. PRN, *pro re nata* (as needed). VIVID: laser, n=132; 2q4, n=136; 2q8, n=135. VISTA: laser, n=154; 2q4, n=154; 2q8, n=151. Full analysis set; LOCF, censoring measurements after rescue treatment was given. [a]p<0.0001 vs. laser. [b]Patients in the laser group were eligible to receive aflibercept PRN from Week 100 if they met predefined vision loss and OCT criteria. [c]The use of aflibercept in this study arm is not in accordance with the licensed posology for aflibercept in DME. [d]The use of aflibercept in this study arm is not in accordance with the recently updated licensed posology for aflibercept in DME, which now allows individualized T&E dosing in the first year. Please consult local guidance. **1.** Heier JS, *et al. Ophthalmology* 2016;123:2376–2385. **2.** Korobelnik J-F, *et al. Ophthalmology* 2014;121:2247–2254. **3.** Brown DM, *et al. Ophthalmology* 2015;122:2044–2052.

Figure 7. DRCR.net Protocol T study in DME: mean change in BCVA from baseline through week 104.

Protocol T:[1]
interventional, randomized, multicenter, head-to-head-to-head study in patients with DME (N=660)

AUC over 2 years:[3]
- Aflibercept: **17.1** (p=0.009 vs. ranibizumab, p<0.001 vs. bevacizumab)
- Ranibizumab: **13.6**
- Bevacizumab: **12.1**



The treatment regimen tested in Protocol T was not the label regimen for either aflibercept or ranibizumab in DME. The licensed dose for ranibizumab ex-US is 0.5mg – the 0.3mg dose of ranibizumab used in this study was not in accordance with the ex-US prescribing information for ranibizumab in DME. Bevacizumab has no marketing authorisation for intravitreal use. AUC, area under the curve. BCVA, best corrected visual acuity. CST, central subfield thickness. DME, diabetic macular edema. ETDRS, Early Treatment Diabetic Retinopathy Study. VA, visual acuity. [a]Injection was withheld if there was no improvement or worsening after two consecutive injections; injection was reinstated if VA score or CST worsened according to treatment protocol. [b]Adjusted treatment group comparison in mean AUC for aflibercept vs. ranibizumab and bevacizumab groups. **1.** Diabetic Retinopathy Clinical Research Network, *et al. N Engl J Med* 2015;372:1193–1203. **2.** Wells JA, *et al. Ophthalmology* 2016;123:1351–1359. **3.** Jampol LM, *et al. JAMA Ophthalmol* 2016. DOI:10.1001/jamaophthalmol.2016.3698.

early, intensive dosing in DME. In the comparative DRCR Network Protocol T study in patients with DME, individualized aflibercept dosing achieved superior vision gains compared with ranibizumab 0.3mg and bevacizumab 1.25mg at the primary endpoint at week 52.[73†] Among patients with baseline VA < 69 letters, vision gains with aflibercept over 2 years were superior to those observed with ranibizumab and bevacizumab (**FIGURE 7**).[74]

In prospective studies (two clinical trials and one interventional study), patients with DME achieved VA gains from baseline with aflibercept T&E, with 63.4%–89.0% reaching ≥q12w dosing intervals in year 1 after early, intensive dosing.[75-77]

The first case presentation described a 63-year-old male type 2 diabetic patient with significant diabetic multi-organ disease and long-standing DME with a significant ischemic component. Baseline BCVA was 20/32 in both eyes and reading vision was poor. Considerations included establishing patient awareness that long-standing edema predicts a delayed treatment response and the need to improve systemic disease control. Treatment was initiated with five monthly aflibercept doses in the right eye. Reading vison significantly improved but distance vision was unchanged and monthly injections were continued due to persisting fluid. Visual acuity improved and near vision remained stable through 2 years. Within 4 years, treatment was extended to q12w dosing intervals, with hyperreflective material and recurrent fluid precluding further extension. This patient achieved significant functional and morphological improvement and illustrates the ability to individualize aflibercept treatment with extended dosing after achieving stabilization in eyes with longstanding DME with a relevant ischemic component.

> Following a treatment switch to aflibercept, visual and anatomic outcomes improved.

The second case report described a 74-year-old male patient with chronic insulin-dependent type 2 diabetes, significant unilateral long-lasting DME and ischemic maculopathy. Baseline BCVA in the right eye was 10/40. At six months, two months after the fifth aflibercept injection, VA improved to 8/20. This patient achieved and maintained a good anatomic and visual response through 2 years, with VA further improving to 12/20 with 14 injections administered.

A proactive individualized approach to treatment with aflibercept is well suited to patients with DME who may experience difficulties with frequent clinic visits, observed Professor Garweg.[8,78,79] Early, intensive treatment and flexible dosing beyond the first year delivers meaningful, long-term vision gains for patients with DME.[18,75]

† The PRN treatment regimen tested in Protocol T was not the label regimen for either aflibercept or ranibizumab in DME. The licensed regimen for aflibercept in DME in the European Union is one injection per month for five consecutive doses, followed by one injection every two months. Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or individualized, such as with a T&E dosing regimen, where the treatment intervals are usually increased by 2-week increments to maintain stable visual and/or anatomic outcomes. The licensed dose for ranibizumab ex-US is 0.5mg; the 0.3mg dose of ranibizumab used in Protocol T was not in accordance with the ex-US prescribing information for ranibizumab in DME. Bevacizumab is not licensed for intravitreal use.

Exploring patient cases in PCV

Presenter: Professor Gemmy Cheung

Polypoidal choroidal vasculopathy (PCV), a subtype of nAMD, is a major cause of vision loss across different patient populations worldwide.[80] Unlike other anti-VEGF agents in PCV, which may require concurrent treatment with photodynamic therapy (PDT) to maximize VA gains, aflibercept monotherapy reduces treatment burden with favorable long-term vision gains.[81–83]

A subgroup analysis of ALTAIR showed improved and maintained functional and anatomic outcomes over 96 weeks in treatment-naïve patients with PCV using a proactive, individualized aflibercept T&E regimen with 2- or 4-week interval adjustments (T&E-2W/T&E-4W).[84] By week 96, 41.3% and 47.7% of PCV patients, respectively, achieved q16w treatment intervals, comparable to durability outcomes seen in the non-PCV subgroup. Additionally, 43.3% overall were maintained on a treatment interval of 16 weeks without interval reduction between week 16 and week 96.[84] Complete polyp regression was reported in 57% of patients in the T&E-2W group and 50% of patients in the T&E-4W group at week 96.

In the PLANET trial of aflibercept monotherapy, overall VA gain from baseline through year 2 was >10 letters, with 41.2% of patients achieving treatment intervals of ≥12 weeks.[83] Several real-world studies also confirm that aflibercept T&E provides potential to extend patients with PCV to q12w dosing and beyond.[85–88]

The first case presentation described was a 57-year-old male patient with baseline BCVA of 20/40. Examination revealed polypoidal lesions on indocyanine green angiography (ICGA), SRF and PED. Following treatment initiation with 3 monthly aflibercept injections, BCVA was maintained at 20/50, SRF and PED subsided and polypoidal lesion resolved. A T&E approach using 2-week interval adjustments up to q12w was then followed through the first year. At one year, BCVA was stable and repeat ICGA showed no recurrence of the polypoidal lesion. Dosing was gradually extended up to q16w during the second year. Vision remained good at 20/40 without the need for additional PDT.

The second case report described a 58-year-old male patient with PCV and baseline BCVA of 20/50 who was initiated on treatment with aflibercept monotherapy. Subretinal fluid resolved and BCVA improved to 20/40 after a monthly loading phase. Treatment was then extended gradually to every 8 weeks (q8w), with vision maintained stable. There was an unexpected delay and the patient returned 9 weeks later with a slight decrease in vision and recurrence of SRF. The dosing interval was shortened to every 4 weeks and vision and fluid were subsequently stabilized once again. Treatment was gradually extended to q8w but was shortened and maintained at every 6 weeks to maintain vision and a dry retina.

"In both cases, we were able to use aflibercept monotherapy to resolve retinal fluid and deliver good visual outcomes," noted Professor Cheung. "We learned that a proactive T&E approach provides the ability to personalize retreatment to meet individual patient needs and characteristics. In conclusion, a proactive, individualized T&E regimen with aflibercept provides potential to extend patients to treatment intervals up to q16w without compromising early vision gains."[17,84]

Exploring patient cases in RVO

Presenter: Professor Sobha Sivaprasad, Moorfields Eye Hospital, UK

Retinal vein occlusion (RVO) is the second most common cause of vision loss due to retinal vascular disease.[89,90] Professor Sivaprasad explained that intravitreal anti-VEGF therapy is the standard of care for treating macular edema in RVO.[91] Expert guidelines recommend individualized dosing regimens and emphasize the importance of early treatment for optimal outcomes.[91]

Treatment with aflibercept in RVO enables extended treatment intervals following initial monthly injections.[4] In the phase 4 CENTERA study, clinically meaningful and significant improvements in functional and anatomic outcomes were achieved with aflibercept T&E in patients with macular edema secondary to central RVO.[58] From baseline to week 76, patients gained an average of four lines of vision (mean ± SD change: +20.3 ± 19.5 letters) with 65.6% of patients gaining at least 15 letters in vision.

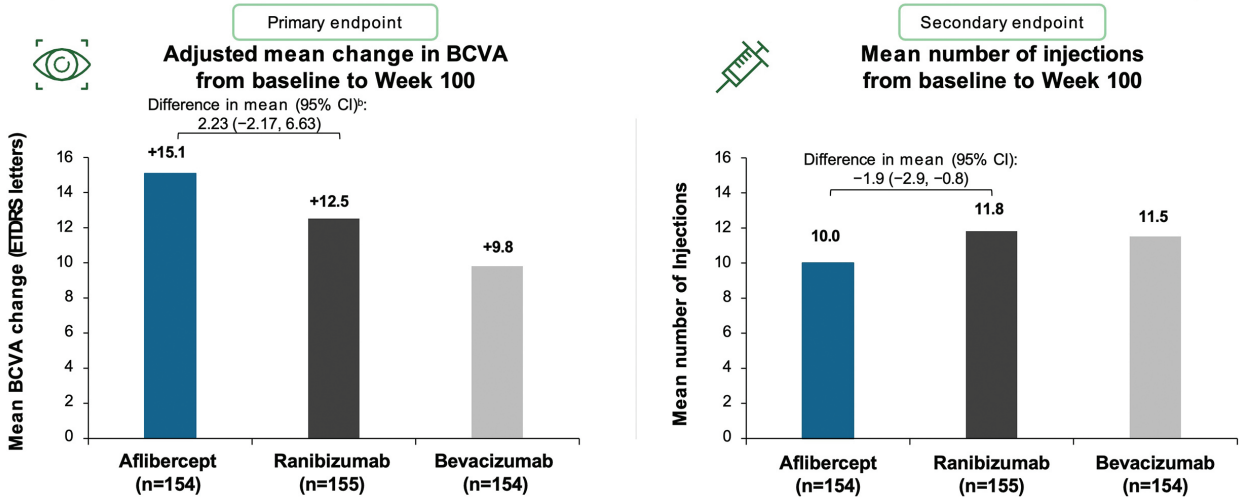
> Expert guidelines emphasize the importance of early treatment of RVO for optimal outcomes.

PLATON, a prospective clinical trial of aflibercept T&E for treatment-naïve macular edema secondary to branch RVO, demonstrated efficacy outcomes comparable to those using a fixed dosing regimen but with reduced treatment burden.[92] From baseline to week 52, the mean ± SD change in BCVA was 23.6 ± 14.2 letters and 73% of patients gained at least 15 letters, with most patients (70.8%) reaching the maximum extension interval of 16 weeks at week 52.

Professor Sivaprasad discussed two case reports of patients

Figure 8. LEAVO: anti-VEGF treatment outcomes in central RVO.

Multicenter, randomized, controlled, non-inferiority, Phase III trial comparing anti-VEGF treatment outcomes[a] in patients with macular edema secondary to CRVO (N=463)



Bevacizumab does not have marketing authorization for intravitreal use. For prescribing and safety profile information for aflibercept 2mg solution for injection, please consult local guidance. BCVA, best corrected visual acuity. CI, confidence interval. CRVO, central retinal vein occlusion. ETDRS, Early Treatment Diabetic Retinopathy Study. ITT, intention-to-treat. RVO, retinal vein occlusion. VEGF, vascular endothelial growth factor. [a]Study eyes were randomised 1:1:1 to intravitreal aflibercept, ranibizumab and bevacizumab. Participants in all study groups had mandated injections at baseline and at Weeks 4, 8 and 12. From Week 16 through Week 96, treatment was given if one or more of the retreatment criteria were met. Visits at Weeks 16 and 20 were mandated; from Week 24, visit interval could be increased from 4 weeks to 8 weeks if retreatment criteria were not met at three consecutive visits. [b]ITT population. Adapted from: Hykin P, *et al. JAMA Ophthalmol* 2019;137:1256–1264.

with central RVO-related macular edema treated with aflibercept as participants in the LEAVO study (**FIGURE 8**).[93]

The first case presentation described a 57-year-old male patient with visual impairment due to early-onset non-ischemic central RVO. At baseline, VA was 59 letters and CST was 1134 µm, the latter a poor prognostic indicator. Treatment was initiated with monthly aflibercept injections. Frequent monthly retreatment was required through 2 years due to persistent edema but the patient's visual acuity improved to 69 letters.

The second case report described a 68-year-old male patient who complained of blurred vision and was diagnosed with ischemic central RVO. Baseline VA was 28 letters and CST was 736 µm. Despite potential for VA improvement being unclear, anti-VEGF treatment was initiated with aflibercept. There was an immediate and rapid improvement in vision and the macular edema completely resolved following the first injection. At month 4, this excellent anatomical outcome was maintained. A further aflibercept injection was given at week 24. Over 2 years, this patient received only 5 injections, CST was stable, the macula was maintained dry and final VA at week 96 was 85 letters. This is a rare example of a patient with ischemic RVO achieving a remarkable VA improvement from baseline with only 5 injections through 2 years, observed Professor Sivaprasad.

HIGHLIGHTS

Symposium Co-Chair: Professor Varun Chaudhary

- Aflibercept 2mg T&E up to q16w strives to improve patient quality of life across exudative retinal disease through balancing reduced treatment burden with preservation of good VA gains.[17,18,87,92]

A vision of the future:
The next level in patient care

Symposium Chair: Professor Nicole Eter, University of Münster, Germany

Symposium faculty looked ahead to consider advancements toward enhanced levels of patient care, including the potential role of novel anti-VEGF formulations, cell and gene therapy and the application of at-home monitoring and artificial intelligence (AI) in ophthalmology practice.

Innovating treatments: Novel approaches with aflibercept

Presenter: Professor Paolo Lanzetta, University of Udine, Italy

Since launch over 10 years ago, aflibercept 2mg has emerged as the standard of care in exudative retinal disease, providing long-term maintenance of clinically meaningful vision gains, with extended treatment intervals, and a well-established safety profile across clinical trials and real-world practice, commented Professor Lanzetta.[17,18,75–77]

Alternative treatment regimens

Recent studies, such as TENAYA and LUCERNE, have explored the potential of alternative treatment regimens that allow extended dosing intervals. In these studies, patients treated with faricimab were assigned to and maintained on fixed q8w, q12w or q16w dosing through week 60 based on disease activity assessment at weeks 20 and 24, with no regimen modification or rescue injections permitted.[48] Faricimab-treated patients with disease activity at week 20 were assigned to and maintained on fixed q8w dosing, while those with disease activity only at week 24 were maintained on q12w dosing. Faricimab-treated patients without disease activity at weeks 20 or 24 were assigned to q16w dosing. Aflibercept 2mg was administered at fixed bimonthly dosing intervals after an initial monthly loading phase.

Patients treated with aflibercept q8w showed rapid improvement of VA from baseline and maintenance of vision gains through month 12.[49] All faricimab dosing interval cohorts showed sustained vision gains throughout the maintenance phase, although increased CST and BCVA variability was noted in the q8w and q12w cohorts.[49]

Continuing to target VEGF and PIGF with novel approaches with aflibercept

Continuing to target VEGF and PIGF may offer potential to improve treatment outcomes and allow for extended dosing regimens, explained Professor Lanzetta. Increasing the initial molar dose of an anti-VEGF agent may offer a longer duration of VEGF suppression and therefore a reduced treatment burden compared with currently available anti-VEGF agents, added Professor Lanzetta.

The phase 2 CANDELA study evaluated an investigational 8mg dose of aflibercept compared to the currently approved 2mg dose of aflibercept in treatment-naïve patients with nAMD. The trial met the primary safety endpoint and no new safety signals were seen through week 44, with the overall safety profile of aflibercept 8mg similar to aflibercept 2mg.[94,95] Investigational aflibercept 8mg is being evaluated in global 96-week phase 3 clinical trials in patients with nAMD (PULSAR) and DME (PHOTON), with participants randomized to receive either aflibercept 8mg q12w or q16w or aflibercept 2mg q8w after a loading phase.

> Increasing the initial molar dose of an anti-VEGF agent may offer a longer duration of VEGF suppression and therefore a reduced treatment burden.

Treating the currently incurable: What is coming next?

Presenter: Professor Francine Behar-Cohen, Paris Descartes University, France

Retinal disease management has rapidly progressed over the past two decades through surgical, imaging and therapeutic revolutions. Advances in therapeutics allow for maintenance or improvement of vision across exudative retinal disease and ocular gene therapy has entered clinical practice.[96–98] Yet despite these striking advances, a proportion of patients with retinal disease still suffer from blindness.[99] Potential reasons are late or insufficient access to diagnosis and/or treatment,

incomplete response to available therapies, incomplete understanding of disease mechanisms and advanced cell death.

Potential avenues under investigation include self-diagnosis and remote follow-up, enhanced anti-VEGF agents, sustained delivery of therapeutic proteins and cell and gene therapy.[50,52,97,98,100,101]

> Cell and gene therapies represent a significant leap forward.... offering potential to reverse severe diseases.

Gene therapy and related approaches show early promise in the treatment of retinal disease, said Professor Behar-Cohen.[55,98,102] Ocular gene replacement trials are underway with new adeno-associated virus (AAV) vectors targeting different retinal gene mutations.[98] Several AAV-based anti-VEGF gene therapy products being investigated in clinical trials are designed for long-term, sustained expression of an exogenous protein.[98] Alternative non-viral gene therapy approaches using naked plasma DNA vectors, antisense oligonucleotides, small-interfering RNAs or microRNA are being explored as potential ocular therapies.[98]

Other novel therapeutic targets are being evaluated to meet unmet needs in retinal disease. Targeting the nitric oxide (NO) pathway using a novel oral sGC enzyme activator is another promising area of research currently being evaluated by Bayer for the treatment of patients with moderately severe to severe non-proliferative diabetic retinopathy.[103,104]

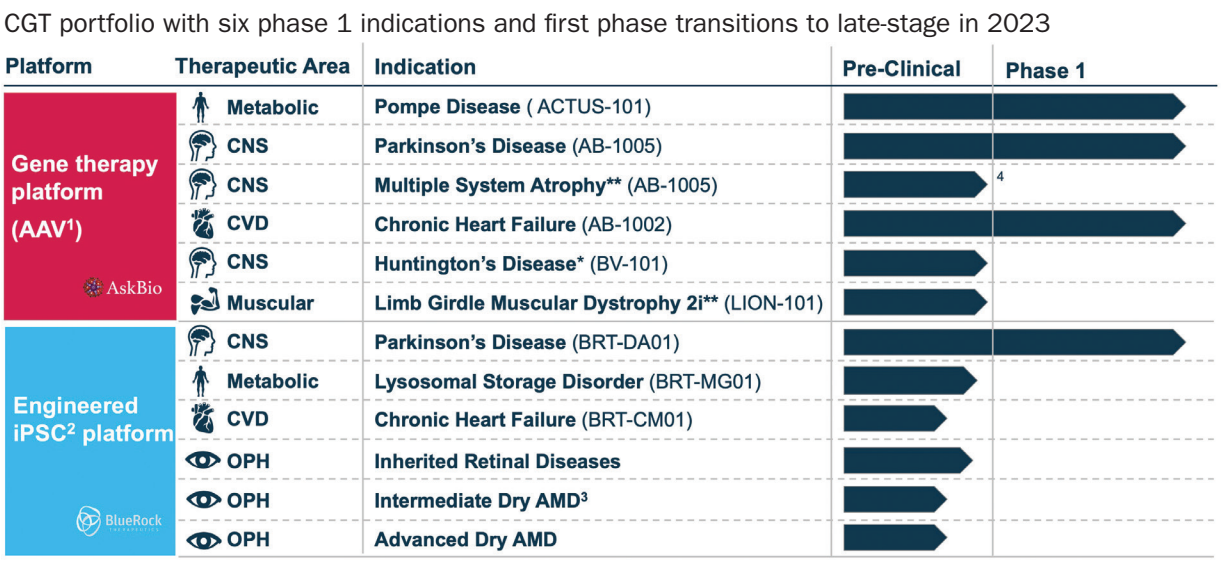
Addressing vision restoration after advanced cell death

Preclinical and early-phase studies investigating cell therapies show encouraging results, indicating the potential to rescue lost photoreceptors and restore damaged retinal tissue, preserving vision.[53]

An ongoing collaboration between Bayer and partners is investigating next-generation cell therapies for AMD and inherited retinal dystrophies, centered on the development of induced pluripotent stem cell (iPSC)-derived photoreceptor and RPE cell therapies. There are three retinal cell therapy programs at preclinical stage focused on inherited retinal diseases, intermediate dry AMD and advanced dry AMD (**FIGURE 9**).[53]

Looking to the future, cell and gene therapies represent a significant leap forward in the evolution of pharmaceuticals, offering potential to reverse severe diseases for the first time, concluded Professor Behar-Cohen. Optogenetics and prosthetic approaches may also provide opportunities to restore function in advanced retinal disease.[55,102,105,106]

Figure 9. Cell and gene therapy development portfolio provides ground-breaking and innovative investigational treatments for patients with debilitating and intractable conditions.



1 AAV = Adeno-Associated Virus; 2 iPSC = induced Pluripotent Stem Cells; 3 AMD = Age-related Macular Degeneration; 4 one patient treated for compassionate use on top of trial cohort
* CTA approved; ** IND granted

Optimizing treatment outcomes through technological innovation

Presenter: Professor Varun Chaudhary, McMaster University, Canada

Most studies of investigational treatments for exudative retinal disease involve noninferiority to aflibercept for VA, commented Professor Chaudhary. "So, it appears we may have reached an upper efficacy threshold of what can achieved for patients with exudative retinal disease. The excitement for me is whether technological advancements can help break through this efficacy ceiling by optimizing treatment outcomes."

Home OCT monitoring and teleophthalmology programs are anticipated to support multiple aspects of patient care and provide important opportunities in ophthalmology practice, particularly with the possibility of early detection of disease activity prior to vision decline and increased precision in monitoring early recurrence, observed Professor Chaudhary.

The most important predictor of long-term vision outcomes is VA at time of presentation. Consistent long-term use of an at-home monitoring system offers a means of increasing early detection of nAMD with good vision.[50,51,107] In the ALOFT study of patients with dry AMD who participated in the ForeseeHome remote telemonitoring program, of the 285 conversions to nAMD while monitored, 52% were detected by device alert.[51] Eyes that converted to nAMD maintained good vision long term with anti-VEGF treatment (VA ≥20/40 in 84% at conversion and 82% at final follow up).

Another study showed that home monitoring with a hyperacuity app was associated with improved visual outcomes and longer treatment retention in patients with nAMD and DME receiving active treatment.[101] Patients using home monitoring had a higher chance of an improvement of ≥5 ETDRS letters at follow-up compared with those not using home monitoring.

> The potential benefits of home monitoring in retinal disease management are significant.

Home OCT offers the possibility of generating new insights into disease dynamics and treatment response in patients with nAMD, offering potential for highly personalized retreatment decisions, added Professor Chaudhary.[52] The phase 4 XPAND clinical trial of aflibercept in patients with nAMD will compare rapid extension T&E (direct to q16w after initial injection at baseline) including at-home OCT monitoring with standard T&E involving 2-week interval adjustment. The primary outcome is BCVA change from baseline to week 36 and the study will continue through week 52.

In summary, the potential benefits of home monitoring in retinal disease management are significant, argued Professor Chaudhary. The application of AI-based technologies may also improve disease detection and monitoring, provide accurate prediction of retreatment need and help guide treatment extension decisions.[108–112]

Improving patient care through holistic disease understanding

Presenter: Professor Anat Loewenstein, Tel Aviv Medical Center, Israel

Professor Loewenstein further underscored the promising role of remote home monitoring, noting that office visits provide only limited insights into disease dynamics and treatment response. Development of OCT systems that can be self-operated by patients at home provides the potential for precise remote monitoring and improved individualized therapy.

Bayer is advancing the understanding of exudative retinal disease and facilitating the sharing of clinical guidance across the globe through education, collaboration and innovation. Ongoing educational initiatives supported by Bayer are striving to advance clinical knowledge, address unmet needs and improve patient care, and create a network of worldwide expertise, noted Professor Loewenstein.

Initiatives led and/or supported by Bayer include the Vision Academy, the Global Retinal Network Program, Real-World Evidence Steering Committee (RWESC) and the nAMD and DR Barometer initiatives. Through education, collaboration and innovation, Bayer is actively engaged in optimizing patient care and improving vision outcomes for all, concluded Professor Loewenstein.

HIGHLIGHTS

Symposium Chair: Professor Nicole Eter

- Investigational aflibercept 8mg may offer potential for further extended durability in a large majority of patients with nAMD or DME while improving and maintaining vision long term.
- Preclinical studies of cell and gene therapies show early promise in the treatment of retinal degeneration.[53,113]
- Home monitoring and AI could optimize treatment outcomes for patients with retinal disease by facilitating early diagnosis, reducing treatment burden, aiding disease monitoring and predicting treatment response.[50,101,110,114]

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Name of the medicinal product: Eylea 40mg/mL solution for injection in pre-filled syringe. Eylea 40 mg/mL solution for injection in a vial. (Refer to full SmPC before prescribing.) **Composition:** One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. Each vial contains an extractable volume of at least 0.1 mL, equivalent to at least 4 mg aflibercept. *Excipients:* Polysorbate 20, Sodium dihydrogen phosphate, monohydrate, Disodium hydrogen phosphate, heptahydrate, Sodium chloride, Sucrose, Water for injection. This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.
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). Eylea is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.
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 for adults: 2 mg aflibercept (0.05 ml) equivalent to 0.05 mL. Recommended dose for preterm infants: 0.4 mg aflibercept (0.01 ml). **Adult indications:** 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. 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 or shorter than 4 weeks 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. Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or individualized, such as with a treat-and-extend dosing regimen, where the treatment intervals are usually increased by 2-week increments to maintain stable visual and/or anatomic outcomes. There are limited data for treatment intervals longer than 4 months. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. Treatment intervals shorter than 4 weeks have not been studied. The schedule for monitoring should be determined by the treating physician. 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. **Preterm infant indication:** For RoP, treatment is initiated with a single injection per eye and may be given bilaterally on the same day. The PICLEO paediatric dosing device in combination with the pre-filled syringe must be used for administration of a single dose of 0.4 mg aflibercept (equivalent to 0.01 mL solution for injection) In total, up to 2 injections per eye may be administered within 6 months of treatment initiation if there are signs of disease activity. The treatment interval between the 2 doses injected into the same eye should be at least 4 weeks.
Contraindications: Hypersensitivity to aflibercept or to any of the excipients. Active or suspected ocular or periocular infection. Active severe intraocular inflammation.
Warnings and Precautions: The warnings and precautions for adults also apply for preterm infants with ROP. The long-term safety profile in preterm infants has not been established. 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. Adult patients must report any symptoms of endophthalmitis or any of the abovementioned events without delay. Patients with ROP should be observed by healthcare professionals for any signs suggestive of endophthalmitis. Parents and caregivers should also be instructed to observe and report any signs suggestive of endophthalmitis without delay. For ROP administration in preterm infants, the pre-filled syringe must be used in combination with the PICLEO paediatric dosing device to avoid a higher than recommended volume that could result in increased intraocular pressure. 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 ≥ 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 ≥ 30 letters compared with last assessment; subretinal haemorrhage involving centre of fovea, or, if size of haemorrhage is ≥ 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: Adult indications: Very common: Visual acuity reduced, Conjunctival haemorrhage, Retinal 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. **Preterm infant indication:** Adverse reactions established for adult indications are considered applicable to preterm infants with ROP, though not all were observed in the ROP Phase III study. Adverse reactions reported in more than one patient treated with aflibercept 0.4 mg in ROP were retinal detachment, retinal haemorrhage, conjunctival haemorrhage, injection site haemorrhage, intraocular pressure increased and eyelid oedema. The long-term safety profile in preterm infants with ROP has not been established.

On prescription only. Marketing Authorisation Holder: Bayer AG, 51368 Leverkusen, Germany.
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