Ophthalmol Ther
https://doi.org/10.1007/s40123-026-01344-x

ORIGINAL RESEARCH

One-Year Real-World Outcomes of Switching to Aflibercept 8 mg in Eyes with Neovascular Age-Related Macular Degeneration: A Swiss Retina Research Network Report

Alice M. Kitay · Anne Tillmann · Isabel Pfister · Christin Schild · Matteo Bonanata · Katharina Heck · Tahm Spitznagel · Felix Gabathuler · Nicolo Bartolomeo · Simon Magnin · Jordan Löliger · Marion R. Munk · Moreno Menghini · Katja Hatz · Gábor Márk Somfai · Sandrine Zweifel · Aude Ambresin · Chiara M. Eandi · Nicolas Feltgen · Andreas Weinberger · Justus G. Garweg · Malaika M. Kurz-Levin

Received: January 6, 2026 / Accepted: February 10, 2026

ABSTRACT

***Introduction*:** This multicenter, longitudinal, observational real-world study evaluated the efficacy and safety of switching to intravitreal aflibercept 8 mg (Afl 8) in pretreated eyes with neovascular age-related macular degeneration (nAMD) within the Swiss Retina Research Network. A total of 283 eyes from 245 patients previously treated with other anti-vascular endothelial growth factor (anti-VEGF) agents (aflibercept 2 mg, faricimab, and ranibizumab) were included, with 1-year efficacy outcomes analyzed in 246 eyes and safety assessed in all treated eyes.

***Methods*:** We recorded demographics, baseline functional and anatomical parameters—including spectacle-corrected visual acuity (VA) and optical coherence tomography (OCT) data—treatment history and outcomes over 12 months after switching to Afl 8. The main outcome measures were change in VA, central subfield thickness (CST), presence of intra- and subretinal fluid (IRF/SRF) and pigment epithelial detachment (PED), treatment intervals, and adverse events.

***Results*:** Twelve months after the switch to Afl 8, mean VA remained stable, while mean CST decreased from 329.1 to 302.8 µm ($p<0.001$).

Alice M. Kitay and Anne Tillmann share the first authorship.

Justus G. Garweg and Malaika M. Kurz-Levin share the last authorship.

Prior Publication: "Early Real-Life Experience with Aflibercept 8 mg in switcher patients suffering from neovascular age-related macular degeneration, A Swiss Retina Research Network Report" presenter Prof A. Ebneter at EURETINA September 5, 2025; "Longer-lasting anti-VEGF drugs for neovascular AMD" presenter Prof. S. Zweifel at FLORetina ICOR December 5, 2025; "Longer-lasting anti-VEGF drugs for neovascular AMD" presenter Prof. S. Zweifel at FLORetina ICOR December 5, 2025; "From Theory to Practice with EYLEA® 8 mg" presenter Prof. Justus G. Garweg at the Annual Turkish Society of Ophthalmology Meeting in Antalya, November 20, 2025; "Aflibercept 8 mg: Herausforderungen in der Schweiz" presenter PD Dr. Weinberger and Prof. Justus G. Garweg at the Ophthalmologische Tagung Olten, January 30, 2026; "Aflibercept 8 mg: One-Year Real-World Data and Robust Efficacy in nAMD in Pretreated Patients" presenter Dr. Alice M. Kitay at Swiss Academy of Ophthalmology Conference February 5, 2026.

A. M. Kitay · M. M. Kurz-Levin
Talacker Augen Zentrum Zürich (TAZZ), Zurich, Switzerland

A. Tillmann · M. R. Munk
Gutblick Practice Group, Pfäffikon, Switzerland

I. Pfister · C. Schild · J. G. Garweg (✉)
Berner Augenklinik and Swiss Eye Institute, Bern, Switzerland
e-mail: justus.garweg@augenklinik-bern.ch

M. Bonanata · M. Menghini
Department of Ophthalmology, Institute of Clinical Neurosciences of Southern Switzerland (INSI), Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland

Published online: 04 March 2026

The portion of eyes without retinal fluid increased from 29.9% at baseline to 47.5% after 12 months. In parallel, the mean treatment interval was extended by 32.3% from 7.1 to 9.4 weeks ($p < 0.001$). At 1 year, 35.4% of eyes reached intervals of 8–11 weeks, while 20.2% achieved intervals of 12 weeks or longer. Intraocular inflammation was reported in 11 cases (3.9%).

Conclusions: In pretreated nAMD eyes with high treatment demand, switching to Afl 8 resulted in a significant anatomical improvement and longer treatment intervals in a majority of patients. These real-world results highlight the therapeutic potential of Afl 8, with no new or unexpected safety issues.

Keywords: Aflibercept; Anti-VEGF; Switcher; Age-related macular degeneration; Retina; Swiss Retina Research Network; Real-world

K. Heck · K. Hatz
Vista Augenklinik Binningen, Binningen, Switzerland

T. Spitznagel · G. M. Somfai
Department of Ophthalmology, Stadtspital Zurich, Zurich, Switzerland

T. Spitznagel · G. M. Somfai
Spross Research Institute, Zurich, Switzerland

F. Gabathuler · S. Zweifel
Department of Ophthalmology, University Hospital Zurich, Zurich, Switzerland

N. Bartolomeo · A. Ambresin
Swiss Visio Montchoisi, Lausanne, Switzerland

S. Magnin · C. M. Eandi
Hôpital Ophtalmique Jules Gonin, Lausanne, Switzerland

J. Löliger · N. Feltgen
University Hospital Basel, Basel, Switzerland

M. R. Munk · J. G. Garweg
Klinik Und Poliklinik Für Augenheilkunde, Inselspital, University of Bern, Bern, Switzerland

M. R. Munk
Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Evanston, USA

G. M. Somfai
Department of Ophthalmology, Semmelweis University, Budapest, Hungary

Key Summary Points

Why carry out this study?

Neovascular age-related macular degeneration (nAMD) often requires long-term, intensive anti-vascular endothelial growth factor (anti-VEGF) therapy, and many pretreated patients continue to show persistent or recurrent retinal fluid with high treatment burden in clinical practice.

Aflibercept 8 mg was designed to provide stronger and more durable VEGF suppression than other agents, potentially improving anatomic outcomes and enabling longer treatment intervals. However, evidence in heavily pretreated, real-world nAMD populations is still limited.

This multicenter, longitudinal, observational study within the Swiss Retina Research Network therefore evaluated 1-year efficacy, durability, and safety after switching pretreated nAMD eyes from other anti-VEGF agents to aflibercept 8 mg in routine clinical practice.

What was learned from the study?

Switching to intravitreal aflibercept 8 mg in previously treated nAMD resulted in anatomical improvement and extended treatment intervals, while maintaining visual acuity and showing no new safety concerns.

Central subfield thickness decreased significantly, with a substantial increase in eyes achieving complete retinal fluid resolution at 12 months.

Treatment burden was reduced, with over half of eyes achieving ≥ 8-week dosing intervals and a favorable safety profile maintained.

C. M. Eandi
Department of Surgical Sciences, University of Torino, Turin, Italy

A. Weinberger
Pallas-Klinik Olten, Olten, Switzerland

INTRODUCTION

Age-related macular degeneration (AMD) is a disease of the central retina characterized by irreversible and progressive destruction of the outer retinal layers. Advanced stages including neovascular AMD (nAMD) and geographic atrophy (GA) are associated with substantial and progressive visual impairment [1–3]. Given the demographic shift towards aging populations, the global prevalence of AMD is expected to increase, reaching 20% in certain regions by 2050 [4]. Intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) treatment is the only therapy demonstrated to prevent vision loss and to stabilize nAMD [1], but the treatment burden associated with this method still represents an unmet medical need limiting long-term functional outcomes for affected patients [5–7].

In large randomized clinical trials (CANDELA and PULSAR), high-dose aflibercept (8 mg; Afl 8) demonstrated superior drying potential and a more durable effect than the marketed comparator drug aflibercept 2 mg, without increased safety signals [8, 9], resulting in its approval by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Swissmedic in 2024, enabling treatment intervals of 16 weeks or greater after disease stabilization [10].

While the PULSAR-3 study demonstrated that Afl 8 may reduce the treatment burden for both patients and healthcare systems, the generalizability of these findings to real-world clinical practice remains limited. The trial enrolled a selective patient population—only treatment-naïve patients with baseline visual acuity between 78 and 24 letters (best-corrected visual acuity [BCVA])—and excluded those with significant comorbid conditions. Moreover, an initial fixed-dosing regimen, followed by interval adaptation based on prespecified activity and inactivity criteria, was adopted under close monitoring, which may not adequately mirror the proactive, adaptive approaches often implemented in real-world settings. In light of these limitations of the PULSAR-3 study, real-world data are of high interest for evaluating the efficacy, durability, and safety of Afl 8 in a more complex and less controlled real-world situation. Thus, it is of particular importance to determine how effectively the new agent performs in this context in a real-world population.

To date, only limited real-world data are available on Afl 8 in nAMD, with most studies reporting small sample sizes and short observation periods. Existing data originate mainly from the United States [11, 12], where the largest series included 219 eyes after an average follow-up of 22.9 weeks [11]. European studies have primarily reported early anatomical and functional outcomes, with follow-up ranging from 3 to 6 months and typically involving small or single-center cohorts (United Kingdom $n = 59$, Germany $n = 83$, Switzerland $n = 10$) [13–15]. Moreover, real-world case series frequently report on mixed populations or treatment-naïve eyes, limiting their applicability to pretreated patients with high treatment demand. Moreover, early post-marketing experience indicates an increased incidence of intraocular inflammation (IOI) under Afl 8, which might limit its clinical application [16–18].

The aim of this study was to evaluate the 1-year efficacy and safety of switching to intravitreal Afl 8 in a Swiss multicenter real-world cohort of pretreated patients with nAMD within the Swiss Retina Research Network (SRRN).

METHODS

This was a national multicenter project with a longitudinal and retrospective observational non-comparative design by the SRRN, including 11 retina clinics in Switzerland (Berner Augenklinik, Bern; Swiss Visio Retina Research Center, Lausanne; Jules Gonin Eye Hospital, University Hospital Lausanne, Lausanne; University Hospital Basel, Basel; Vista Augenklinik Binningen, Binningen; Talacker Augen Zentrum Zürich, Zürich; Istituto Neuroscienze cliniche della Svizzera Italiana [INSI], Ente Ospedaliero Cantonale [EOC] Lugano, Switzerland; Augenarzt Praxisgemeinschaft Gutblick, Pfäffikon, Switzerland; Stadtspital Zürich, Zürich; Pallas Kliniken, Olten; University Hospital Zürich, Zürich).

The study was approved by the Swiss Ethics Committee of the canton of Berne (registration/BASEC no. 2024-01026) based on the general consent of all included patients to use their anonymized data for this analysis. Moreover, the study adhered to the International Council for Harmonisation E6 Good Clinical Practice Guideline, the Declaration of Helsinki in its latest version, and federal laws.

All patients presented with active nAMD requiring frequent intravitreal anti-VEGF therapy with aflibercept 2 mg, faricimab, or ranibizumab following a treat-and-extend (T&E) protocol. The inclusion period ranged from April 1, 2024, to August 31, 2024, during which patients were switched to Afl 8. To be included, patients were required to have a minimum follow-up of 11 months after the first Afl 8. Both eyes were included if both met the inclusion criteria for this study, i.e., a Snellen BCVA at or above 0.1 at the time of diagnosis. All eligible eyes were consecutively included within each participating center during the inclusion period.

Exclusion criteria were subretinal bleeding > 1 optic nerve head (ONH) diameter at diagnosis, pretreatment with photodynamic therapy (PDT), or any opacification in the optic axis with relevance for visual function prohibiting ocular imaging and fundoscopy. Patients with any preexisting structural damage to the macula for any other reason without functional potential or any systemic comorbidities interfering with the treatment outcomes, namely any local or systemic rheumatoid diseases and/or vasculitis requiring treatment, were excluded from the study. Patients who discontinued Afl 8 before 12 months—due to adverse events, switching therapy, or other reasons—remained included for the duration of their treatment; their data were incorporated up to the time of discontinuation. If patients underwent cataract surgery during the study period, BCVA data were censored to minimize an inherent bias. Any other intraocular surgery or laser treatment within 3 months prior to inclusion in the study was an exclusion criterion, except YAG laser capsulotomy.

All patients were treated using a T&E regimen beginning with the last pre-switch interval but without a formal loading phase after switch. Treatment intervals were extended or shortened based on disease activity, guided primarily by OCT findings, with adjustments generally made in 2-week increments at the discretion of the treating physician. The same physician applied a consistent T&E protocol before and after switching, and the principles did not differ between anti-VEGF agents. In this context, disease activity was defined based on the presence of intra- and subretinal fluid (IRF/SRF) and dynamics of pigment epithelial detachment (PED). If retinal fluid was newly observed within the central 6 mm circle of the ETDRS (Early Treatment Diabetic Retinopathy Study) grid, or if fluid at any location increased, disease activity was assumed and the treatment interval adopted accordingly.

Data were extracted from the electronic medical records. Chronological dates of interest were the time of diagnosis and start of anti-VEGF therapy, after 3 months, 6 months before switching to Afl 8, the last anti-VEGF injection before switch, switch to Afl 8, and 1, 3, 6, and 12 months after switching to Afl 8. Baseline measurements were defined as those obtained at the time of switch, corresponding to the visit of the first Afl 8 injection. VA and OCT parameters were recorded immediately before this injection. A minimum of three injections with another anti-VEGF agent prior to switch to Afl 8 was required for an eye to be defined as pretreated.

We collected Snellen refracted VA, intraocular pressure (IOP) and the following OCT parameters: central subfield thickness (CST), presence of IRF, SRF, and PED within a macular radius of 1 and 6 mm as defined by the ETDRS grid in OCT, macular atrophy and macular neovascularization (MNV) lesion type. For statistical reasons, VA was converted from Snellen VA to ETDRS letters, with a Snellen VA of 1.0 corresponding to 85 ETDRS letters.

Primary outcomes were change in VA and CST over time as well as change in injection intervals from the switch to Afl 8 to the last injection 12 months after. Secondary outcomes included change in fluid dynamics between switch and 1, 3, 6, and 12 months thereafter as well as adverse events.

Data were analyzed using IBM SPSS version 27 software (IBM Corp., Armonk, NY, USA) and R (version 3.2.4; R: A language and environment for statistical computing, R Foundation for

Statistical Computing, Vienna, Austria, 2016). We used descriptive statistics and non-parametric tests for the analysis, since the Shapiro–Wilk test revealed that the data were not normally distributed. Data are presented as mean ± standard deviation (SD), median, and interquartile ranges (IQR: 25–75%). The Wilcoxon signed-rank test was applied for paired data and the Friedman test for repeated measures. Comparisons in subgroup analyses were made with the Mann–Whitney *U* test. Results of regression analyses are presented as follows: *r* (degrees of freedom) = the *r* statistic, *p* = *p* value. Missing values were not substituted or imputed; analyses were conducted on the available cases only. Safety was evaluated using descriptive summaries of both ocular and non-ocular adverse events, including death, up to the conclusion of the study. Statistical significance was defined as a p value < 0.05.

RESULTS

Demographics

A total of 283 eyes from 245 pretreated patients with active nAMD were included in the analysis. Patients who started Afl 8 treatment after August 2024 were not part of the primary analysis population. Among the included eyes, 246 completed at least 12 ± 1 months of follow-up and were analyzed for the primary efficacy outcome (Fig. 1), while all 283 eyes were included in the safety analysis. A total of 38 patients (15.5%) had both eyes treated. Demographic and baseline data are presented in Table 1.

Injections

The mean number of injections prior to switch was 33.0 ± 27.6, and the mean treatment

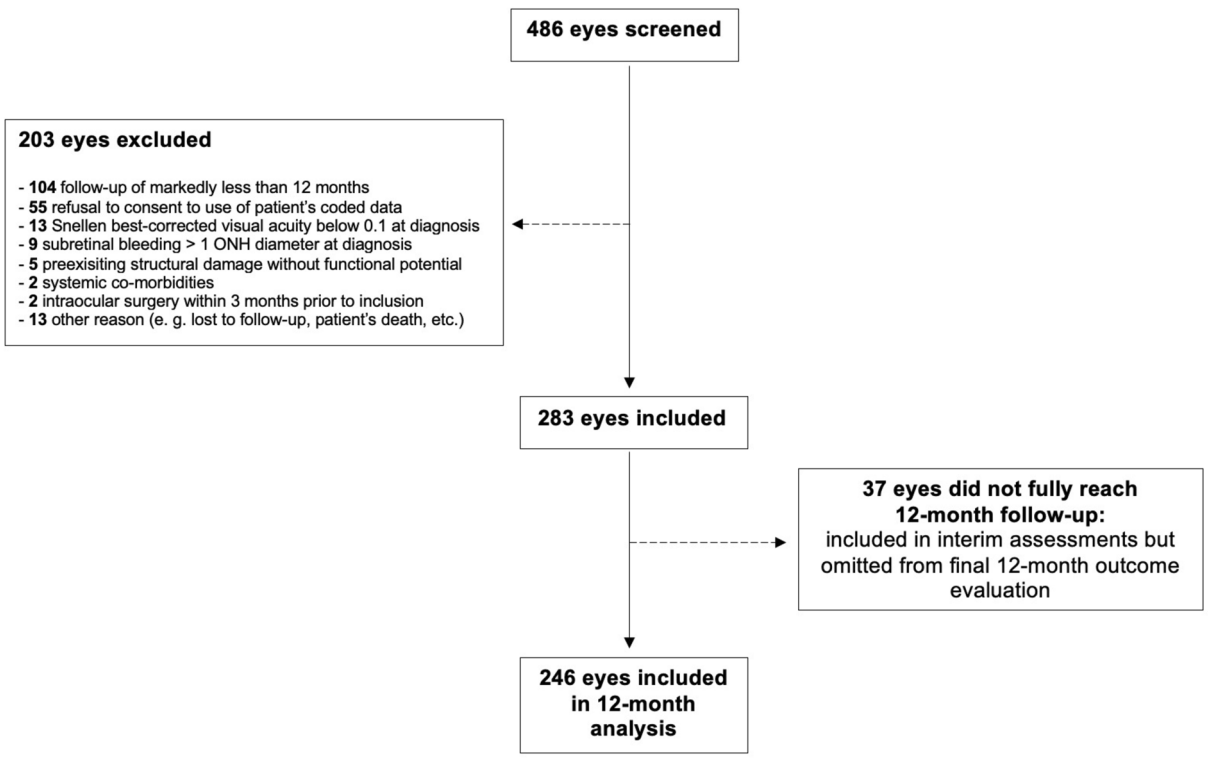

Fig. 1 Inclusion and exclusion flow diagram with overview of exclusion reasons. ONH: optic nerve head

Table 1 Baseline and demographic data of the study population ($n = 283$)

Patient demographics		
	Number	**%**
Total eyes (patients)	283 (245)	
Sex		33.9
Male	83	66.1
Female	162	
Median [IQR]		
Age (years)	81.0 [77.0, 86.0]	
Baseline clinical features		
Mean treatment duration until switch (in years) (mean ± standard deviation, median, IQR)	4.1 ± 3.2 (3.3, 1.5–5.8)	
Last medication injected before switch		
Aflibercept 2 mg	199 (70.3%)	
Faricimab	73 (25.8%)	
Ranibizumab	11 (3.9%)	
Reason for switch		
Persistent activity on Q4W	131 (46.3%)	
Fluid recurrence on extension	91 (32.2%)	
Switch with aim to extend despite sufficient response	57 (20.1%)	
Other (treatment reuptake, pause)	3 (1.4%)	
Mean treatment interval before switch	7.1 ± 2.7 (6.9, 5.0–8.0)	
MNV type		
Type 1	167 (59.0%)	
Type 2	45 (15.9%)	
Type 1/2, mixed	15 (5.3%)	
Type 3	18 (6.4%)	
PCV	10 (3.5%)	
Macular atrophy at switch	92 (45.1%)	
BCVA (ETDRS)	69.5 ± 15.7 (75.0, 65.1–80.2)	
Central retinal thickness (μm)	314.5 ± 120.6 (291.0, 233.0–366.0)	
Presence of PED	148 (72.5%)	
Maximal PED height in the central 3 mm (μm)	201.0 ± 123.0 (161.0, 113.0–242.0)	
Presence of macular fluid	197 (70.1%)	
Subretinal	113 (40.2%)	
Intraretinal	61 (21.7%)	
Both SRF/IRF	23 (8.2%)	

BCVA best-corrected visual acuity, *ETDRS* Early Treatment of Diabetic Retinopathy Severity score, *IQR* interquartile range, *IRF* intraretinal fluid, *PED* pigment epithelium detachment, *MNV* macular neovascularization, *PCV* polypoidal choroidal vasculopathy, *Q4W* every 4 weeks, *SRF* subretinal fluid

duration before switch was 4.1 ± 3.2 years. Pre-switch treatment included aflibercept 2 mg (70.3%), faricimab (25.8%), and ranibizumab (3.9%). The most common reasons for switch to Afl 8 were (1) "poor responders" to previous anti-VEGF therapy (46.3%), defined as persistent IRF or SRF despite monthly injections; (2) "frequent flyers," defined as recurrence of fluid at treatment intervals ≤ 8 weeks despite repeated extension attempts (32.5%); and (3) switch with the attempt of achieving longer treatment intervals despite anatomical response and treatment intervals of more than 8 weeks (20.5%).

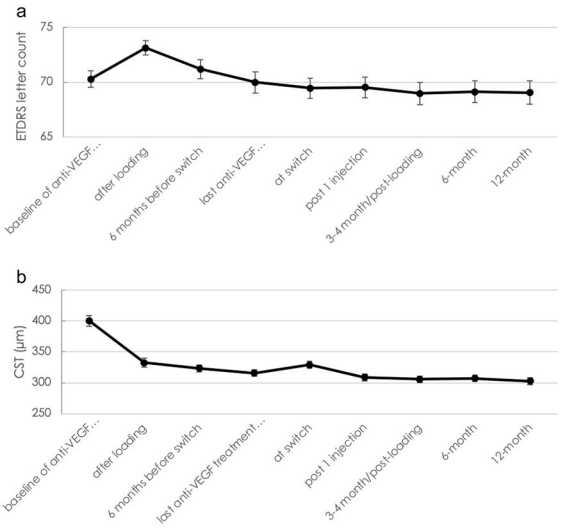

Fig. 2 **A**, **B** Changes in mean best-corrected visual acuity (BCVA) (**A**) and central subfield thickness (CST) (**B**) from baseline of anti-VEGF therapy to 12-month follow-up. After treatment with aflibercept 8 mg, a significant change in CST (**B**) at 12 months is observed, while BCVA does not show a significant difference from switch

Primary Outcomes

VA in ETDRS letters remained stable from the time point of switch to 12 months (at switch 69.5 ± 15.7, median 75.0, IQR: 65.1–80.2; 12 months after switch 69.1 ± 16.0, median 73.9, IQR: 65.1–80.2; change of 0.3 ± 10.2 ETDRS letters, $p = 0.58$ (Fig. 2A).

CST in µm was reduced significantly from the time point of switch to 12 months (at switch 329.1 ± 91.3, median: 308.0, IQR: 271.0–363.0; 12 months after switch 302.8 ± 85.1, median 287.0, IQR: 248.3–330.8; change of 22.0 ± 75.6 CST in µm, $p < 0.001$ (Fig. 2B).

At switch, 84 eyes (29.9%) showed no retinal fluid in the foveal 1 mm zone. A total of 134 (50.6%) were completely dry 1 month after the first Afl 8 injection. After 12 months of Afl 8 therapy, no retinal fluid was present in the foveal 1 mm in 114 eyes (47.5%) (Fig. 3).

Treatment interval improved significantly after the switch: The last interval prior to the switch was 7.1 ± 2.7 weeks, which improved to 9.4 weeks ± 5.6 after 12 months ($p < 0.001$). At the time of switch, 42 (14.8%) eyes required injections every 4 weeks, whereas 12 months after switching to Afl 8, only 19 eyes (6.7%) still required 4-week intervals.

Subgroup comparison based on prior anti-VEGF agent:

Among the 283 included eyes, 199 had received aflibercept 2 mg and 73 faricimab as their last treatment before switching. Within these groups, 89 versus 40 eyes were classified as poor responders, respectively. Given these subgroup sizes, comparative analysis was feasible only for poor responders. Eyes last treated with faricimab had a significantly longer pre-switch treatment duration (5.4 ± 2.7 vs. 3.3 ± 3.1 years; $p < 0.001$). During the first year after switching to Afl 8, they required more injections (9.6 ± 1.7 vs. 8.3 ± 1.9; $p < 0.001$) and remained on shorter intervals (7.0 ± 3.8 vs. 8.7 ± 4.9 weeks; $p = 0.012$). A dry macula at 1 year was achieved more frequently in the aflibercept 2 mg subgroup (44.1% vs. 25%).

Secondary Outcomes:

Adverse events were observed in 14 eyes (4.9%) following the switch to Afl 8 (see Table 2). Among these, 11 eyes (3.9%) developed IOI, manifesting as anterior or intermediate uveitis. One case occurred after the first Afl 8 injection. Five cases developed 3–4 months after the switch; all five eyes had received three injections before the event. Three additional IOI cases occurred within the first 6 months, after

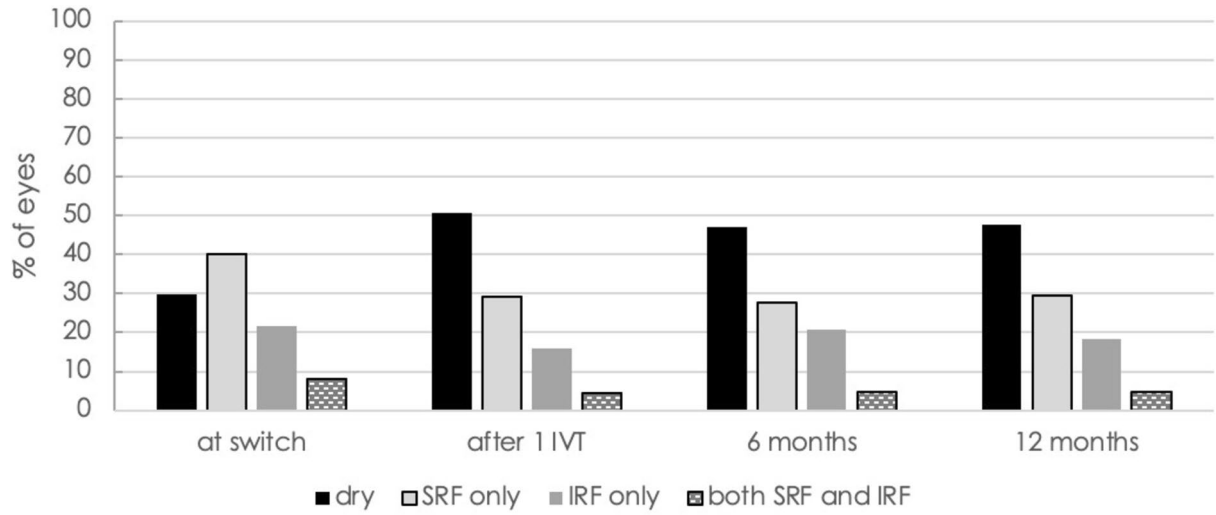

Fig. 3 Macular fluid status at switch, after the first aflibercept 8 mg injection, and after 6 and 12 months. The proportion of eyes displaying a dry macula on optical coherence tomography increases markedly over time, from 29.9% at switch to 47.5% at 12 months. *IRF* intraretinal fluid, *SRF* subretinal fluid

Table 2 Adverse events following switch to aflibercept 8 mg treatment ($n = 283$)

Adverse event	Cases (*n*, %)
Intraocular inflammation	11 (3.9%)
Intraocular pressure elevation	2 (0.7%)
Retinal pigment epithelium tear	1 (0.4%)

six injections in one eye and after five injections in the other two. The remaining two IOI cases presented within the first year, after 11 and 8 injections, respectively. All cases recovered fully under topical therapy. Seven cases switched to aflibercept 2 mg and three cases to faricimab, while one case remained on Afl 8. No instances of vasculitis were reported. Elevated intraocular pressure was observed in two patients, with one case requiring paracentesis to achieve pressure control. Additionally, one case of retinal pigment epithelial (RPE) tear was documented after the first Afl 8 injection. In all three cases, treatment with Afl 8 was continued.

During the 12-month follow-up, 40 eyes (14.1%) discontinued treatment with Afl 8. Of these, 33 eyes (82.5%) were switched to another anti-VEGF agent, including faricimab ($n = 21$, 63.6%), aflibercept 2 mg ($n = 8$, 24.2%), and ranibizumab ($n = 4$, 12.1%). Thirteen cases (39.4%) were switched because of adverse events in the study eye, 15 (45.5%) because of insufficient response, three (9.1%) because of patients' own wish to switch, and two (6.1%) due to an adverse event (AE) in the fellow eye. In five eyes (12.5%), therapy was stopped completely, while in two additional eyes (5.0%), discontinuation was related to patient health issues.

DISCUSSION

In this multicenter, real-world cohort of pretreated patients with nAMD, we report the anatomical and functional outcomes following a switch to Afl 8 over a 12-month period. To date, only limited real-world data are available for Afl 8 in nAMD, with most studies reporting small patient numbers and observation periods of maximally 6 months [10–14]. Registration trials such as PULSAR exclusively enrolled treatment-naïve patients, a group not fully representative of those treated in routine clinical practice [9]. In clinical practice, in contrast, newly approved anti-VEGF agents are first offered to patients with a treatment history of persistent or frequently recurring disease activity, highlighting

the importance of real-world evidence for assessing their efficacy and safety in clinical routine [19]. With the aim of narrowing this gap, the cohort of pretreated patients with nAMD in this study reports outcomes in eyes incompletely responsive to previous therapy. The principal motivation for switching in this context is to enhance disease control and alleviate the treatment burden. Indeed, switching to Afl 8 resulted in improved control of disease activity and reduced treatment demand in these challenging cases without relevantly compromising safety.

Our data demonstrate that switching to Afl 8 can achieve relevant anatomical improvement, with a mean CST reduction of 22 ± 75.6 µm after 1 year. While this reduction is notable, it is distinctly smaller than the CST decreases reported in the PULSAR trial (mean CST change: 142 µm for q12 [every 12 weeks] dosing and 147 µm for q16 dosing at week 48) [9]. This difference is clearly attributable to the effect of pretreatment in our cohort, the proactive T&E treatment approach, and eyes being less responsive to anti-VEGF treatment. Supporting this, the PULSAR extension trial found that patients who switched from 2 to 8 mg aflibercept at week 96 showed an additional CRT decrease of only 10 µm up to week 156 [20]. Comparison with early real-world data reveals a consistent pattern regarding anatomical outcomes after switching to Afl 8. Bala et al. conducted a large single-center US study ($n = 219$, pretreated 209) and observed a nonsignificant CST decrease of 6.4 µm after a follow-up of 22.9 weeks ($p = 0.356$), reflecting stabilization rather than substantial improvement in a heavily pretreated cohort [11]. Similarly, a UK study with 59 pretreated eyes found no significant CST change over 33.5 weeks, although a significant reduction in PED height was reported [13]. Sambhara et al. reported a significant average CST decrease of 39.4 µm over 6 months (21.5 µm for pretreated eyes), in close agreement with our own results at this time point [12]. Another case series noted significant reductions in both PED height and CST after three injections (follow-up: 4 weeks post-loading), but 10 out of 61 patients were treatment-naïve, which influenced the magnitude of the response [14]. Two artificial intelligence (AI)-based studies in treatment-naïve patients reported significant early anatomical improvements following Afl 8 treatment. In one small study ($n = 10$), mean CST reductions of 87 µm and 96 µm were observed after 1 and 3 months, respectively [15]. Similarly, in a larger cohort from Lausanne ($n = 51$), mean CST decreased significantly by approximately 108 µm at month 6 [21], consistent with the PULSAR findings.

Together, these real-world studies consistently show that significant structural improvements under Afl 8 are more pronounced in treatment-naïve eyes, while those with prior anti-VEGF exposure, and hence longer disease activity, tend to stabilize or only modestly improve in CST and related metrics. In real life, the balance between optimizing the response to treatment and treatment burden typically drives therapeutic decisions, i.e., the change in treatment intervals following a T&E protocol. Given that functional gains are typically widely limited in pretreated eyes, the chance for interval extension was preferred to a potential anatomical improvement in our cohort. Consequently, the anatomical response in our cohort was accompanied by substantial extension of treatment intervals, increasing from 7.1 to 9.4 weeks on average from switch to 12 months. Musadiq et al. similarly observed a significant extension of the mean treatment interval in a cohort of 59 pretreated patients, from 7.7 to 8.7 weeks over a mean follow-up of 33.5 weeks [15]. The interplay between longer dosing intervals and fewer injections marked a significant relief in treatment burden, mirroring the promising durability and flexibility of Afl 8 observed in PULSAR, where 83% of patients maintained intervals of ≥ 12 weeks at week 48 [9]. In contrast, Bala et al. reported that a considerable proportion of patients (46.6%) were unable to extend treatment intervals to ≥ 8 weeks due to persistent macular fluid; the average follow-up period in that cohort was 22.9 weeks [11]. In our cohort, only 20.2% of patients achieved treatment intervals of ≥ 12 weeks at the 1-year mark, while 44.4% remained on intervals < 8 weeks, and 35.4% were maintained between 8 and 11 weeks ($n = 243$ with available data) (Fig. 4). These proportions closely mirror those reported by Bala et al. [11]. This variation in treatment response across studies can be largely attributed

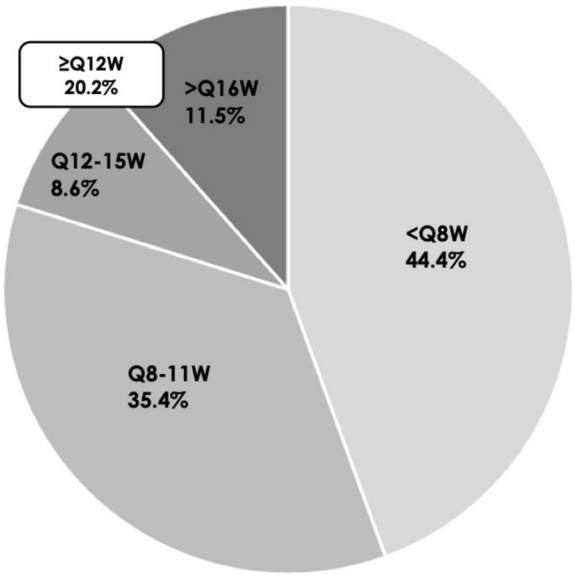

Fig. 4 Distribution of treatment intervals 12 months after treatment with aflibercept 8 mg

to differences in treatment protocols and patient management approaches. Unlike the fixed and protocol-driven regimens employed in pivotal trials, where patients typically received three loading doses followed by mandated extension intervals (12 or 16 weeks) and therefore a set number of injections—around six in the first year—real-world practice in switchers is characterized by individualized treatment adaptation.

In our study, the last treatment interval was 7.1 ± 2.7 weeks prior to switch and 9.4 weeks ± 5.6 after 12 months, indicating a more flexible and individualized treatment approach. This contrasts with the more relaxed protocols often applied in real-world studies, where injection frequencies are typically lower than in randomized controlled trials [22]. The proactive strategy used here aimed to maximize visual performance under a T&E protocol. A central methodological consideration affects the evaluation of disease activity: While pivotal phase 3 trials tend to rely on fluid status assessed exclusively within the central foveal 1 mm in combination with a functional improvement/stability and decline [8, 9], ophthalmologists in real-world environments typically do not pay maximal attention to the disease-inherent changes in BCVA but review the entire macular OCT scan and also intervene early if fluid is present outside the central foveal mm [23]. This broader perspective on anatomical changes can lead to quicker reinjection and thus shorter interval extensions relative to standardized trial protocols. Additionally, real-world cohorts include all patients with nAMD, namely those with more complex or refractory disease profiles compared to the highly selected populations in randomized trials, resulting in generally shorter achievable treatment intervals. In clinical practice, adherence to therapy and follow-up can be more variable in routine practice, and concurrent comorbidities may complicate disease management, both factors contributing to less optimal treatment results in real-world settings [19]. As short treatment intervals (< 8 weeks) were frequently applied in this cohort, it should be acknowledged that reimbursement policies and healthcare system constraints vary across countries, which may affect the generalizability of these findings.

In contrast to the PULSAR trial, which reported a gain in visual acuity (+6.7 for q12 and +6.2 for q16 at week 48) [9], our real-world population did not experience a significant improvement in BCVA after 1 year of Afl 8. The absence of relevant visual acuity gains in our cohort—as outlined above—is linked to the pretreated status and extended disease duration of eyes in our cohort, which is often associated with advanced structural changes such as macular atrophy and fibrosis [24]. Additionally, the higher baseline VA in our population (68.2 letters) relative to PULSAR (59.6 letters) may have introduced a ceiling effect, further explaining the limited functional gains after switching therapy.

Stable BCVA values observed over 12 months reflect published experience for pretreated patients with nAMD in general, with a frequently prolonged disease history including atrophy [23, 25]. Recent real-word outcome reports confirm the absence of a significant VA change after switch to Afl 8 [10–13].

The observed discrepancy between anatomical and visual outcomes underscores the complexity of treating long-standing nAMD and highlights a possible role of early switch prior to encountering permanent structural retinal changes. Moreover, these results emphasize the

need for tailored treatment approaches in long-term managed patients and the importance of considering baseline characteristics such as disease duration, previous therapeutic exposure, and structural changes as predictors of functional outcomes of switching.

Regarding safety, our cohort exhibited a rate of IOI of 3.9%, which is notably higher than the rate of 0.7% reported in the PULSAR trial. While several smaller real-world studies did not observe IOI after Afl 8 [13–15], several other groups reported incidence of IOI between 3% and 10% [16–18]. Importantly, in all these instances—including our own—all cases of IOI resolved completely with topical therapy. To date, only one case of occlusive vasculitis under Afl 8 has been published [26].

This study has several inherent limitations. Beyond the retrospective observational design, potential differences in treatment protocols across centers—such as re-treatment criteria—may have introduced a bias. In addition, the decision to transition patients to Afl 8, including timing and treatment intervals, was left to the discretion of individual retina specialists. While this reflects real-world clinical practice, it inevitably resulted in variability in patient management. Such heterogeneity should be considered when interpreting the results, as it may affect both treatment outcomes and the generalizability of our findings. Furthermore, a potential bias may result from the selection of patients switched to Afl 8 because of incomplete response to other anti-VEGF therapies or because of the personal preference of the physician and patients. The heterogeneity of prior treatment exposure to different anti-VEGF agents could also have affected treatment demand and response to Afl 8. The follow-up period of 12 months provides short- to medium-term outcomes, which must not be considered predictive for longer-term durability, safety, or adherence. The inclusion of both eyes in bilaterally affected cases without correction for inter-eye correlation violates the assumption of independence underlying the applied statistical tests (Wilcoxon signed-rank test and Friedman test) and thus may have resulted in an—albeit from our perspective, minor—overestimation of treatment effects. Finally, the retrospective nature of data collection may have led to underreporting of adverse events and did not permit evaluation of broader functional or patient-reported outcomes. These factors should be considered when extrapolating the results to other clinical settings.

CONCLUSION

In this multicenter real-world study, switching to Afl 8 in pretreated nAMD led to meaningful anatomical improvement, stable visual acuity, and reduced treatment burden for a substantial proportion of patients. While the overall safety profile was reassuring and aligned with previous reports, the observed rates of intraocular inflammation highlight the need for continued monitoring. Importantly, our data indicate that, despite the potential for extended dosing intervals reported in clinical trials, a significant portion of pretreated eyes—especially those with persistent macular fluid—still require frequent injections. In summary, our results demonstrate the value of Afl 8 as an interesting therapeutic option for a complex real-world patient population, while emphasizing the need for ongoing real-world evidence and tailored management strategies.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Author Contributions. Concept of the study: Justus G. Garweg, Isabel Pfister, Christin Schild. Design of the study: Justus G. Garweg, Isabel Pfister, Christin Schild. Substantial contribution to data acquisition: Alice M. Kitay, Anne Tillmann, Isabel Pfister, Christin Schild, Matteo Bonanata, Katharina Heck, Tahm Spitznagel, Felix Gabathuler, Nicolo Bartolomeo, Simon Magnin, Jordan Löliger, Malaika M. Kurz-Levin, Marion M. Munk, Moreno Menghini, Katja Hatz, Gabor Márk Somfai, Sandrine Zweifel, Aude Ambresin, Chiara M. Eandi, Nicolas Feltgen, Andreas Weinberger, and Justus G. Garweg. Statistical analysis: Justus G. Garweg, Isabel Pfister,

Christin Schild. Drafting of the manuscript: Anne Tillmann, Alice M. Kitay, Isabel Pfister, Malaika M. Kurz-Levin, Marion M. Munk, Justus G. Garweg. Review of the manuscript: all authors. Final approval: all authors.

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest. Justus G. Garweg: Advisor and speaker for several pharmaceutical companies. Contributes to several international industry-sponsored clinical studies in the fields of retinal disease and uveitis (AbbVie, Bayer, Novartis, Roche). This manuscript is independent of these activities. Marion R. Munk: Consultant for AbbVie, Allergan, Acucela, Aviceda Therapeutics, Alimera, Bayer, LumiThera, OD-OS, Isarna Therapeutics, Roche, Novartis, Oculis, OcuTerra, genesight Therapeutics, Kubota, Böhringer-Ingelheim, EyePoint, Ocular Therapeutix, Apellis, Astellas, Zeiss, RetinAI, Dandelion. Andreas Weinberger: Payed consultant and/or lecturer for AbbVie, Apellis, Bayer, Roche, Sandoz. Sandrine Zweifel: Consultant and advisor for Alcon, Allergan, Apellis, Bayer, Endogena, Novartis, Roche, and Zeiss and grant support from Bayer, Novartis, and Roche outside the submitted work. Gabor Márk Somfai: consultant for Apellis, Allergan, Astellas, Bayer, Carl Zeiss, Roche. Nicolas Feltgen: Consultant and lecturer for Apellis, Bayer, Novartis, Roche, Heidelberg Ing. Katja Hatz: Advisory board participant and lecturer for Apellis, Bayer, Roche, AbbVie/Allergan, Novartis; contract research and/or grant support for Bayer, Roche, AbbVie/Allergan, Novartis. Moreno Menghini: consultant for Alcon, Apellis, Astellas, Bayer, and Roche. Lecturer for Bayer and Roche. Grant support from Bayer and Roche. Aude Ambresin: consultant for Bayer, Novartis, Roche, Apellis, and EarlySight; lecturer fees from Optovue, AbbVie, Novartis, Bayer, Roche, Apellis, Astellas, and RetinAI. Chiara M. Eandi: advisory board participant and lecturer for AbbVie, Apellis, Astellas, Bayer, and Roche. Alice M. Kitay, Anne Tillmann, Isabel Pfister, Christin Schild, Matteo Bonanata, Katharina Heck, Tahm Spitznagel, Felix Gabathuler, Nicolo Bartolomeo, Simon Magnin, Jordan Löliger, and Malaika M. Kurz-Levin have nothing to disclose.

Ethical approval. The study was approved by all participating ethics committees, led by the Ethics Committee of the canton of Berne (registration no. 2024–01026). Coded patient data were included based on general or specific informed consent, in line with the International Council for Harmonisation Good Clinical Practice (ICH-GCP) E6 guidelines, the Declaration of Helsinki, and Swiss law.

REFERENCES

1. Fleckenstein M, Schmitz-Valckenberg S, Chakravarthy U. Age-related macular degeneration: a review. JAMA. 2024;331(2):147–57.

2. Bressler NM. Age-related macular degeneration is the leading cause of blindness. JAMA. 2004;291(15):1900–1.

3. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol. 2010;10:31.

4. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. Lancet. 2012;379(9827):1728–38.

5. Semeraro F, Morescalchi F, Duse S, Parmeggiani F, Gambicorti E, Costagliola C. Aflibercept in wet AMD: specific role and optimal use. Drug Des Devel Ther. 2013;7:711–22.

6. Papadopoulos Z. Aflibercept: a review of its effect on the treatment of exudative age-related macular degeneration. Eur J Ophthalmol. 2019;29(4):368–78.

7. Lim JI, Ko S, McAllister M, Faux N, Bawa K, Mearns E, et al. Systematic review of clinical practice guidelines for the management of neovascular age-related macular degeneration. Eye Lond. 2025;39(11):2223–30.

8. Wykoff CC, Brown DM, Reed K, Berliner AJ, Gerstenblith AT, Breazna A, et al. Effect of high-dose intravitreal aflibercept, 8 mg, in patients with neovascular age-related macular degeneration: the phase 2 CANDELA randomized clinical trial. JAMA Ophthalmol. 2023;141(9):834–42.

9. Korobelnik JF, Lanzetta P, Leal S, Holz FG, Clark WL, Eichenbaum D, et al. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration: 96-week results from the randomized phase 3 PULSAR trial. Ophthalmology. 2025.

10. Lanzetta P, Korobelnik JF, Heier JS, Leal S, Holz FG, Clark WL, et al. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial. Lancet. 2024;403(10432):1141–52.

11. Bala S, Barbosa GCS, Mohan N, Srivastava SK, Kaiser PK, Sastry A, et al. Initial functional and anatomical outcomes of high-dose aflibercept 8 mg in exudative neovascular age-related macular degeneration. Ophthalmol Retina. 2025;9(8):756–66.

12. Sambhara D, Vakharia P, Eichenbaum DA. Real-world efficacy and safety of 8 mg aflibercept in neovascular AMD: a case series. BMJ Open Ophthalmol. 2025. https://doi.org/10.1136/bmjophth-2024-002091.

13. Musadiq M, Musadiq M, Latif F, Ng B, Azzopardi M, Gilead N, et al. Early real-world outcomes of switching to 8 mg aflibercept for neovascular age-related macular degeneration in the United Kingdom. Life. 2025. https://doi.org/10.3390/life15060903.

14. Grün M, Rothaus K, Lommatzsch AP, Faatz H. [Erste Real-World-Erfahrungen mit Aflibercept 8 mg bei der Behandlung der neovaskulären AMD]. Klin Monbl Augenheilkd. 2025.

15. Cattaneo J, De Oliveira Figueiredo EC, Montesel A, Vermeirsch S, Eandi CM. Early real-world outcomes of intravitreal aflibercept 8 mg in treatment-Naïve neovascular AMD: AI-assisted fluid volume analysis. Int J Retina Vitreous. 2025;11(1):42.

16. Binder KE, Bleidißel N, Charbel Issa P, Maier M, Coulibaly LM. Noninfectious intraocular inflammation after intravitreal aflibercept. JAMA Ophthalmol. 2025;143(6):499–506.

17. Hoffmann L, Michels S, Eandi C, Karam MA, Figueiredo ECO, Hatz K. Aflibercept high-dose (8mg) related intraocular inflammation (IOI) - a case series. BMC Ophthalmol. 2024;24(1):520.

18. Nowroozzadeh MH, Hajipourkhorasani M. Increased risk of retinal vasculitis may be associated with aflibercept 8 mg: a pharmacovigilance analysis of the FAERS database. Ocul Immunol Inflamm. 2025;33(6):1056–8.

19. Borkar DS, Parke DW 2nd, Lee AY. Leveraging real-world evidence to enhance clinical trials. Ophthalmology. 2024;131(7):756–8.

20. Wong TY. Aflibercept 8 mg in neovascular AMD: 156-week results from the PULSAR extension. Macula Society Meeting; Florida, USA2025, February. p. https://share.google/iRquNgeVVhLAB2UMO.

21. Bartolomeo N, Schuetz YP, Nascimbeni AC, Castro DG, Crozat B, Barry MP, et al. Early outcome analysis of intravitreal aflibercept 8 mg treatment in Naïve patients with neovascular age-related macular degeneration using artificial intelligence. Ophthalmol Ther. 2025. https://doi.org/10.1007/s40123-025-01239-3.

22. Ciulla TA, Huang F, Westby K, Williams DF, Zaveri S, Patel SC. Real-world outcomes of anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration in the United States. Ophthalmol Retina. 2018;2(7):645–53.

23. Grimaldi G, Ambresin A, Pfister IB, Schild C, Plasencia C, Hatz K, et al. One-year outcomes after switching to faricimab in eyes with pretreated neovascular age-related macular degeneration: a swiss retina research network report. Ophthalmol Retina. 2025.

24. Okeagu CU, Agrón E, Vitale S, Domalpally A, Chew EY, Keenan TDL. Principal cause of poor

visual acuity after neovascular age-related macular degeneration: age-related eye disease study 2 report number 23. Ophthalmol Retina. 2021;5(1):23–31.

25. Arcinue CA, Ma F, Barteselli G, Sharpsten L, Gomez ML, Freeman WR. One-year outcomes of aflibercept in recurrent or persistent neovascular age-related macular degeneration. Am J Ophthalmol. 2015;159(3):426-36.e2.

26. Sisk RA. Occlusive retinal vasculitis after aflibercept 8 mg injection for wet macular degeneration. Retin Cases Brief Rep. 2025.