





# Additional Effects of Faricimab in Aflibercept Low-Responders: Retinal Morphology and Function in Eyes with Neovascular Age Related Macular Degeneration Following a Switch Between Two Anti-VEGF Agents

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**Purpose:** To assess how transitioning from an Aflibercept to a Faricimab intravitreal treatment impacts retinal structures and functional aspects in patients with neovascular age related macular degeneration (nAMD) in a real-life setting.

**Patients and Methods:** A retrospective clinical study including 49 patients (57 eyes) with nAMD at the Department of Ophthalmology and Optometry, Kepler University Hospital, Linz, Austria was performed. The patients, who had previously been receiving monthly Aflibercept injections with an unsatisfactory treatment response, were switched to intravitreal Faricimab and followed-up between 12/2022 and 12/2023.

**Results:** The mean treatment-interval before the fifth injection with Faricimab was  $5.35 \pm 1.49$  weeks and was therefore significantly longer compared to the monthly interval with Aflibercept ( $p < 0.001$ ). Mean baseline central retinal thickness (CRT) was  $267.82 \pm 76.00$   $\mu\text{m}$  and decreased significantly already at month 1 to  $249.61 \pm 65.35$   $\mu\text{m}$  ( $p < 0.001$ ). After the fourth intravitreal injection, there was no significant change with a CRT of  $252.95 \pm 56.96$   $\mu\text{m}$  ( $p = 0.134$ ). There was a significant reduction in the number of patients showing subretinal fluid (SRF) and intraretinal fluid (IRF). In eyes with fibrovascular pigment epithelium detachment (PED), an interval extension was not possible in more than half of the cases. Eyes with serous and drusenoid PED and a rather high amount of hyper-reflective foci (HRF), the majority showed a significant response after the switch.

**Conclusion:** An initial loading dose could be beneficial to elongate Faricimab's additional effect of reducing retinal swelling in eyes with nAMD and previous low-response to Aflibercept. Serous and drusenoid PEDs seem to benefit more than fibrovascular PEDs. A high amount of intraretinal HRF in patients with PED was a sign for good response to Faricimab.

**Keywords:** ARMD, wet age-related macular degeneration, anti-VEGF therapy, Faricimab

## Introduction

Age-related macular degeneration (AMD) represents one of the most common causes of blindness in advanced age in industrialized countries.<sup>1</sup> In the neovascular subtype of AMD (nAMD), choroidal and macular neovascularization lead to abnormal exudation of fluid in the sub- or intraretinal space causing vision loss and functional restrictions to photoreceptors.<sup>2</sup>

The gold standard treatment in patients with nAMD is the anti-vascular endothelial growth factor (anti-VEGF) intravitreal therapy. Different variants of anti-VEGF agents such as Ranibizumab, Bevacizumab and Aflibercept demonstrated pivotal advancement in visual and structural outcomes in the treatment of nAMD.<sup>3–6</sup>



However, there are significant inter-individual differences in the response to anti-VEGF therapy. In clinical practice, visual acuity (VA) and retinal morphology in optical coherence tomography (OCT) mainly determine and classify the treatment's effectiveness.

Recently, Faricimab, a bi-specific antibody targeting VEGF-A and angiopoietin-2 (Ang2) receptors, was approved by the Food and Drug Administration (FDA) for the treatment of nAMD and diabetic macular edema (DME). The additional pathway regulating Ang-2 impacts the vascular permeability and vessel stability. The TENAYA and LUCERNE clinical trials proved that the effect on best-corrected visual acuity (BCVA) in eyes treated with 6 mg of Faricimab was comparable to eyes treated with 2 mg of Aflibercept. The results suggested that Faricimab may lead to an extension of treatment intervals.<sup>7–10</sup>

However, the two clinical trials included only treatment-naïve nAMD patients, whereas in clinical practice many patients with nAMD are in ongoing intravitreal treatment with other anti-VEGF agents.<sup>8</sup>

Therefore, the purpose of our study was to evaluate morphological and functional retinal changes following a switch to Faricimab in patients, who were previously defined as low responders to Aflibercept receiving monthly treatment in a treat and extend regimen.

## Materials and Methods

### Ethical Approval and Consent

This retrospective, single-center study was approved by the institutional review board of Johannes Kepler Universität Linz (EK Nr: 1012/2024) and conducted in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments.

Consent was waived because the study was retrospective and adhered to standard of care treatment for the patient without introduction of any additional risk.

### Procedure

In the study, we analyzed 57 eyes from 49 patients with nAMD at the Department of Ophthalmology and Optometry, Kepler University Hospital, Linz, Austria, between 12/2022 and 12/2023. The patients were switched to Faricimab during this period, and the endpoint of data analysis for this study was 12/2023. All eyes showed low-response to Aflibercept, as the treatment interval could not be extended to more than 4 weeks in a so called “Treat-and-Extend” protocol. In our real-life clinical setting, we define low-response as recurrent or increase in intra- or subretinal fluid after extending beyond a 4-week treatment interval.

Generally, in the “Treat-and-Extend” protocol of the Department, patients received treatment at every visit. The treatment interval was extended by 2 weeks, if there was no sign of intra- or subretinal fluid in OCT (SD-OCT; Heidelberg Engineering). If there were signs of choroidal neovascularization (CNV) re-activation, the interval was reduced by 2 weeks. Minimum interval was 4 weeks, maximum 12 weeks.<sup>11</sup> According to the protocol, following two 12-week-intervals further treatment was discontinued, but patients were further followed.

Following the switch to Faricimab, the previous four-week-interval was maintained between baseline visit and V2. Later-on, further injection intervals were adjusted according to protocol. Baseline findings were defined as the measurements on the first day of an intravitreal Faricimab injection.

The morphological outcomes assessed with OCT included central retinal thickness (CRT), presence and type (fibrovascular, serous, or other) of a pigment epithelium detachment (PED) and the type of fluid (subretinal and / or intraretinal fluid) at baseline and before each treatment with Faricimab. The values for CRT were derived from the central part of the ETDRS grid using Heyex Version 2.5.5 (Heidelberg Engineering GmbH, Heidelberg, Germany).

The amount of hyperreflective foci (HRF) was graded by certified readers into two groups: rather high HRF versus rather low HRF. Independently, the morphological response in the OCT was evaluated by graders based according to a modified version of the model by Amoaku et al (1 = good, 1.5 = rather good, 2 = partial, 2.5 = low, 3 = non-response).<sup>12</sup>

Furthermore, best-corrected visual acuity (BCVA) was analyzed as a functional outcome and the change of treatment intervals was analyzed.

## Statistical Analysis

Statistical analysis was performed using SPSS Version 29.0.0 (IBM Corp, Armonk, New York, NY, USA). The visual acuity (Snellen eye chart) was converted into logMAR for statistical analysis. After assessing normal distribution using the Shapiro–Wilk test, parametric paired data was analyzed using paired *t*-test and one-way analysis of variance (ANOVA). Non-parametric data was evaluated using Mann–Whitney test. A *p*-value of <0.05 was considered statistically significant.

## Results

This study included 57 eyes of 49 patients (19 male, 30 female) with a mean age of  $76.60 \pm 7.18$  years. Patients had received a mean of  $23.98 \pm 16.89$  injections of other anti-VEGF agents prior to Faricimab treatment (Table 1). In the observation period of the first 12 months Faricimab was available in Europe, the patients received an individual number of injections ranging from 2 to 8 injections following a treat and extend protocol.

The mean treatment-interval before the fifth injection (V5) with Faricimab was  $5.35 \pm 1.49$  weeks and was significantly longer compared to the prior monthly interval with Aflibercept ( $p < 0.001$ ). The interval between the second and the third injection (V3) was  $5.15 \pm 1.55$  weeks, and between the third and the fourth injection (V4)  $5.23 \pm 1.58$  weeks (Table 2).

**Table 1** Demographic Characteristics of the Study Sample

Demographic Characteristics	
Age (years), mean $\pm$ SD	76.60 $\pm$ 7.18
Eyes, n (%)	
– Right	27 (47.37%)
– Left	30 (52.63%)
Sex, n (%)	
– Male	37 (64.91%)
– Female	20 (35.09%)
Prior injections, mean $\pm$ SD	23.98 $\pm$ 16.89

**Table 2** Overview of Clinical and Morphological Data

Clinical & Morphological Data	Baseline	V2	V3	V4	V5
Interval (weeks), mean $\pm$ SD	–	4.16 $\pm$ 0.37	5.15 $\pm$ 1.55	5.23 $\pm$ 1.58	5.35 $\pm$ 1.49
BCVA (logMAR), mean $\pm$ SD	0.30 $\pm$ 0.36	0.29 $\pm$ 0.36	0.26 $\pm$ 0.31	0.29 $\pm$ 0.36	0.32 $\pm$ 0.41
CRT ( $\mu$ m), mean $\pm$ SD	267.82 $\pm$ 76.00	249.61 $\pm$ 65.35	256.37 $\pm$ 58.91	258.51 $\pm$ 63.83	252.95 $\pm$ 56.96
SRF, n (%)	28 (49.12%)	9 (15.79%)	19 (35.19%)	16 (35.56%)	10 (25.64%)
IRF, n (%)	23 (40.35%)	12 (21.05%)	15 (27.78%)	13 (28.89%)	12 (30.77%)

The baseline BCVA was logMAR 0.30 ± 0.36. There was no statistically significant improvement in mean BCVA following one injection (logMAR 0.29 ± 0.36; *p* = 0.469) and after four injections (logMAR 0.32 ± 0.41; *p* = 0.340) as shown in Figure 1.

Before the first treatment with Faricimab, the mean baseline CRT was 267.82 ± 76.00. CRT decreased significantly following the first Faricimab to 249.61 ± 65.35 μm (*p* < 0.001). However, following 4 injections there was no significant change in mean CRT 252.95 ± 56.96 μm (*p* = 0.134) compared to baseline CRT detectable (Figure 2).

SRF was present at baseline in 28 eyes (49.12%) and IRF in 23 eyes (40.35%). After the first treatment with Faricimab, the number of patients showing SRF (9 eyes, 15.79%; *p* < 0.001) or IRF (12 eyes, 21.05%; *p* < 0.001) decreased significantly. Following the fourth injection, 10 eyes showed SRF (25.64%; *p* < 0.001 compared to baseline) and 12 eyes IRF (30.77%; *p* = 0.002 compared to baseline).

Twenty-eight eyes (49.12%) had a fibrovascular PED. In these eyes with fibrovascular PED, 53.57% could not be extended to more than 4 weeks according to the described “Treat-and-Extend” protocol. Whereas in eyes with serous (11 eyes; 19.30%) or drusenoid (7 eyes; 12.28%) PED, an initial interval extension without relapse was possible in 81.82% and 85.71%, respectively.

Rather, high amounts of HRF were present in 10 eyes (17.54%), and rather low amounts of HRF in 47 eyes (82.46%). Comparing these two groups according to morphological response to Faricimab, the group with rather high amounts of HRF had a significant better response with a grading of 1.25 ± 0.425 compared to 1.68 ± 0.679 in the group with lower amounts of HRF (*p* < 0.05).

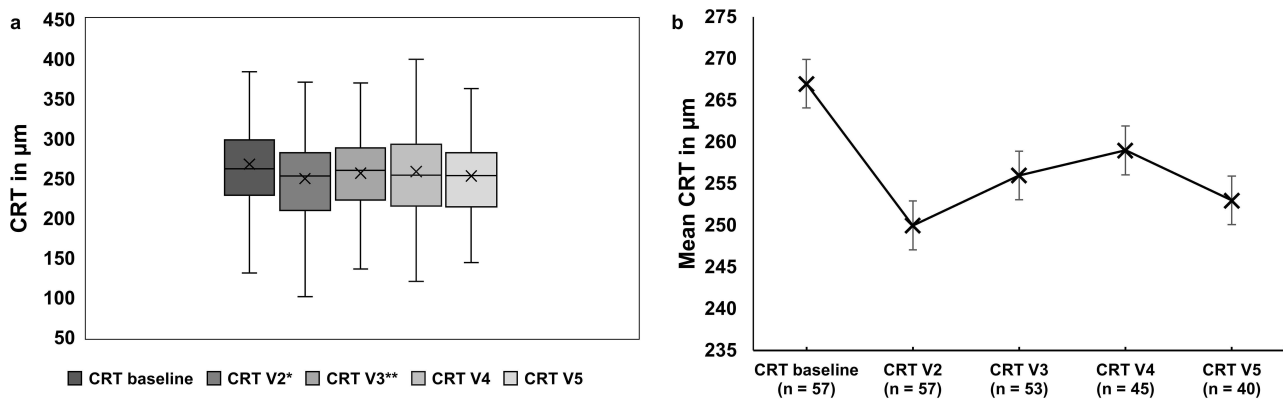


Figure 1 (a) Boxplot for BCVA (logMAR) with x marking the mean BCVA (\**p* < 0.001; \*\**p* < 0.05). (b) Changes in mean BCVA (logMAR) with initial improvement of BCVA, followed by a decline in BCVA.

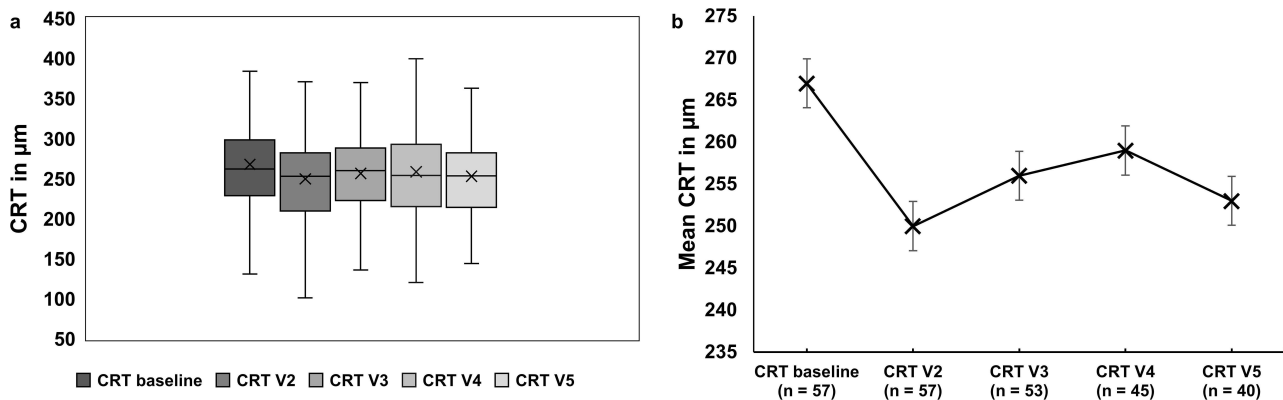


Figure 2 Baseline and time course after the first intravitreal Faricimab injection. (a) Boxplot of CRT (in μm) with x marking the mean CRT. (b) Changes in mean CRT (in μm).

## Discussion

In this study, patients with nAMD and low response to prior monthly aflibercept treatment following a treat and extend regimen were examined after a switch to Faricimab in a real-world setting. Faricimab induced a significant additional morphological improvement in terms of retinal thickness reduction and a reduction in the number of patients showing SRF and/or IRF. As opposed to the treatment with Aflibercept, the treatment intervals could be extended significantly throughout the first year. However, a recurrence of retinal thickening and an increase in the number of patients showing SRF and IRF in the end of the first year indicate that this initial effect could not be maintained and intervals had to be adjusted. Interestingly, there was no significant functional treatment effect throughout the first year. In patients with PED showing a low amount of intraretinal hyper-reflective foci (HRF), Faricimab did not induce a significant additional morphologic effect or increase of the treatment interval.

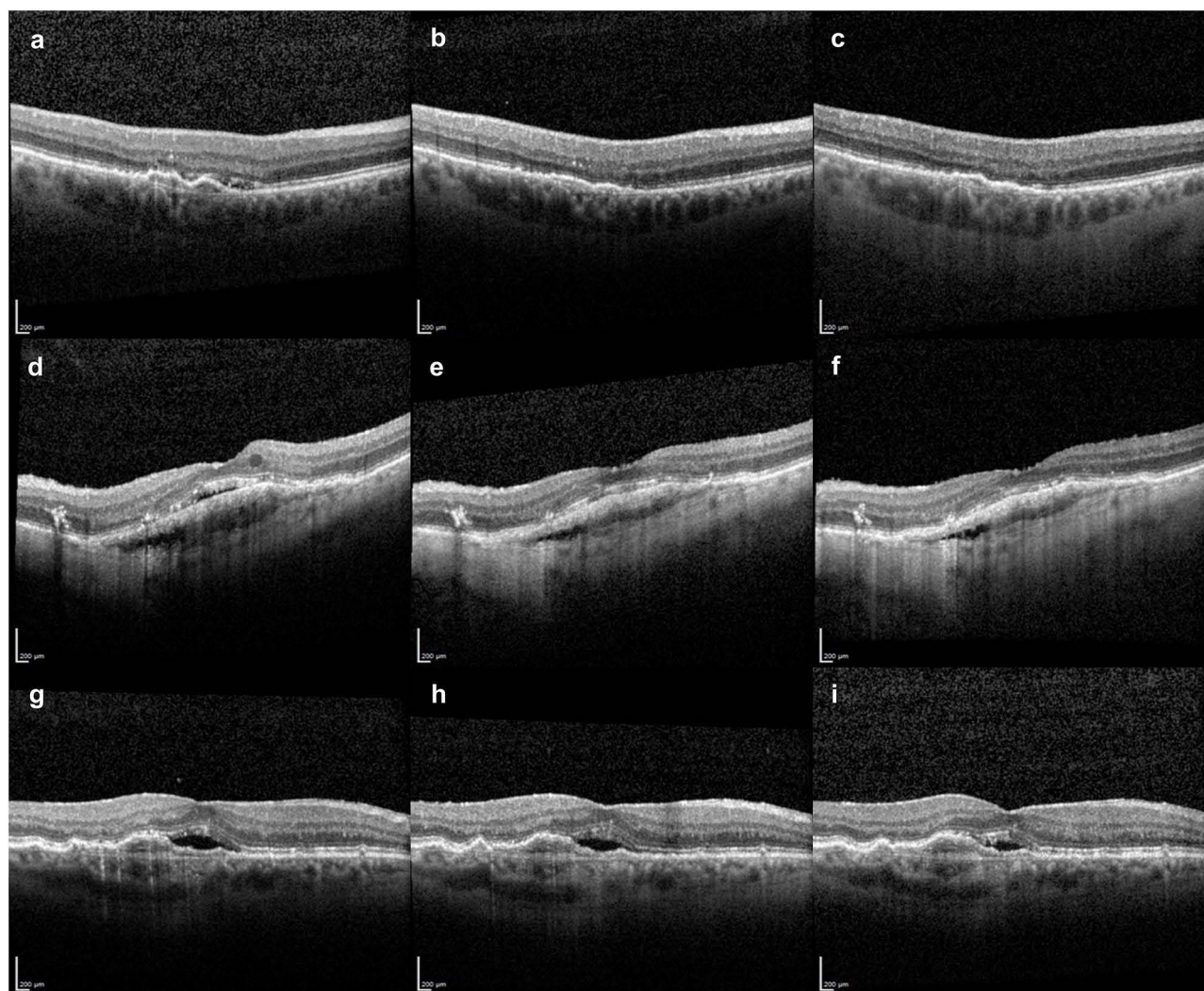
This study assessed morphological and functional retinal changes following a switch from intravitreal Aflibercept to intravitreal Faricimab treatment based on a treat and extend regimen. This study focused on patients showing low response to the Aflibercept therapy as a monthly treatment interval could not be extended due to persistent signs of exudation. Following the initiation of the Faricimab therapy, CRT decreased significantly ( $p < 0.001$ ). However, at the end of the observation period, the change in mean CRT compared to baseline values did not reach a level of significance anymore ( $p = 0.134$ ) in the actual interindividual treatment interval. Accordingly, the number of patients showing SRF and/or IRF decreased after treatment initiation but increased again throughout the observation period. This paradox effect may have been caused by the interval extension itself, even if it was only extended if there was no sign of SRF, IRF, new formation of PED or bleeding. A so-called loading dose of 3 or 4 intravitreal injections with Faricimab could have prevented this paradox effect. Another explanation could be a tolerance effect that has previously reported for intravitreal agents by several groups.<sup>13–15</sup>

According to Amoaku et al, the response to intravitreal treatment in nAMD can be classified in four groups depending on the BCVA and retinal morphology in OCT: good response, partial response, poor response and non-response. In their opinion, reasons leading to poor or non-responsiveness can be multifactorial including tachyphylaxis, increased clearance, chronicity of the disease, genetic profile or metabolic eg drug absorption.<sup>12,15</sup> Yang et al provided a framework with three main areas of potential causes for treatment-resistance to anti-VEGF injections. They differentiated between clinical causes in the diagnosis of nAMD, pharmacological causes of treatment-resistance and other pathogenic ways than VEGF in the formation of neovascularization.<sup>16</sup> Even if it is not possible to draw any conclusions from our data to these explanations, they might at least in part explain the outcomes of our study.

It has to be emphasized that there was no significant improvement in mean BCVA throughout the observation period despite the significant morphologic changes. This might reflect the chronicity of treatment-refractory nAMD leading to persistent macular changes, eg retinal atrophy, photoreceptor damage or fibrovascular scarring. Accordingly, baseline BCVA was rather poor as opposed to registry trials. Nevertheless, the results of this study are consistent with others that did not find a significant improvement in BCVA after switching to Faricimab in therapy-refractory eyes, either.<sup>9,13,17,18</sup>

The chronicity of therapy-refractory nAMD may also be reflected in the presence of pigment epithelium detachments detected in the study cohort. Stanga et al reported a significant flattening of PED after the first Faricimab injection.<sup>19</sup> In our study, analyzing the subgroups of PED, we found that especially serous and drusenoid PED in combination with SRF and/or IRF were a good prognostic factor regarding an interval extension. Whereas in eyes with fibrovascular PED, more than half of the eyes had a reoccurrence of intra- or subretinal fluid after interval extension to six weeks in the treat and extend regimen. Therefore, an initial loading-dose with three injections should be considered in eyes with fibrovascular PED.

Apart from that, in this subgroup of patients showing a PED, a high amount of intraretinal hyper-reflective foci seemed to be a valuable biomarker for an active exudation on the one hand and a good treatment response in terms of treatment-induced retinal thinning by Faricimab on the other. [Figure 3](#) shows OCTs of patients with rather high and low amounts of intraretinal HRF and accordingly good or low response to Faricimab treatment. However, it has to be mentioned that a good response to Faricimab did not automatically induce an equivalent increase of the treatment interval ( $4.67 \pm 0.89$  weeks). HRF have been reported for the very first time by one of the authors of this study (M.B.) to be



**Figure 3** Three OCTs of each patient with rather high and low amounts of HRF. The first OCT before the first Faricimab injection. The second OCT four weeks after the first Faricimab. The third OCT before the fourth Faricimab injection. (a–c) Right eye of a patient with rather high amounts of HRF and a good response to Faricimab with a treatment interval extension to 8 weeks before the fourth Faricimab injection. (d–f) Left eye of a patient with rather high amounts of HRF and a good response to Faricimab with a treatment interval extension to 8 weeks before the fourth Faricimab injection. (g–i) Right eye of a patient with rather low amounts of HRF and a low response to Faricimab with treatment interval extension remaining at 4 weeks before the fourth Faricimab injection.

a valuable sign of vascular leakage, which is in good standing with the correlation of the presence of HRF and therapeutic effects secondary to Faricimab in this study cohort (see Figure 3).<sup>20</sup> As these HRF might serve as a valuable biomarker, an automated HRF quantification using polarization sensitive OCT or artificial intelligence based algorithms may be helpful.<sup>21,22</sup> However, it must be mentioned that in this study, the presence of high HRF amounts was graded by certified readers and not further quantified.

Regarding the treatment interval extension, the cohort of this study did not receive a loading dose with Faricimab as mentioned above. The treatment intervals were adapted according to a treat and extend regimen after the second injection with Faricimab. All patients had a prior 4-week-interval with Aflibercept before switching to Faricimab. In the observation period, the mean treatment-interval was  $5.35 \pm 1.49$  weeks indicating a significant prolongation of the treatment interval ( $p < 0.001$ ). Kishi et al reported a possible extension of injection intervals from  $5.9 \pm 1.5$  to  $7.5 \pm 2.3$  weeks. This suggests that switching to Faricimab is not only reasonable in treatment-refractory eyes.<sup>18</sup>

Limitations of this study include its retrospective nature, small number of patients and a relatively short follow-up period. Further studies with longer follow-up periods and larger study populations are required to evaluate the effect and optimal timing of switching to Faricimab in therapy-refractory nAMD eyes. Nevertheless, it has to be mentioned that this

study is the first real-world report of a clearly characterized patient cohort treated in Austria as soon as Faricimab was available.

## Conclusion

In conclusion, the findings of this study have significant implications for switching from Aflibercept to Faricimab treatment in patients previously low-responding to Aflibercept. Results reveal that patients with serous and drusenoid PEDs in combination with SRF and IRF seem to benefit more than those with fibrovascular PEDs in combination with SRF and IRF. A high amount of intraretinal HRF in patients with PED indicated exudation and, consequently, a good response to Faricimab treatment. Despite significant morphological improvement and a positive effect on the treatment intervals, no significant functional improvement was observed in this study cohort.

## Abbreviations

nAMD, neovascular age-related macular degeneration; CRT, central retinal thickness; SRF, subretinal fluid; IRF, intraretinal fluid; PED, pigment epithelium detachment; HRF, hyperreflective foci; VEGF, vascular endothelial growth factor; VA, visual acuity; OCT, optical coherence tomography; FDA, Food and Drug Administration; BCVA, best corrected visual acuity; DME, diabetic macular edema.

## Data Sharing Statement

Data are available upon reasonable request from the corresponding author.

## Ethics Approval

This retrospective, single-center study was approved by the Ethics committee of the Johannes Kepler Universität Linz (EK Nr: 1012/2024) and conducted in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments.

## Consent for Publication

Patient consent for publication is not applicable.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

MB: Roche (Consultant); JR, ME, HK: No financial competing interests.

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