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Extended-Interval Outcomes with Aflibercept 8 mg in Neovascular AMD: Real-World Evidence from Naïve and Switch Cohorts-The INDIA study

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Abstract

Purpose:

To evaluate the safety, efficacy and durability of intravitreal aflibercept 8 mg in treatment-naïve and previously treated patients with neovascular AMD of South Asian origin in a real-world clinical setting.

Methods:

This retrospective, multicenter observational study included adult patients with neovascular AMD (nAMD) and polypoidal choroidal vasculopathy (PCV) who received intravitreal aflibercept 8 mg in routine clinical practice. Both treatment-naïve patients and those switched from prior anti-VEGF therapy (faricimab or brolucizumab) were included. All patients completed 52 weeks of follow-up. The primary endpoint was the incidence and characterization of treatment-emergent adverse events (TEAEs). Secondary endpoints included changes in best-corrected visual acuity (BCVA), central retinal thickness (CRT), proportion of eyes achieving clinically meaningful visual gains, changes in PED height, SFCT thickness, and treatment interval extension over one year.

Results:

82 patients (82 eyes) with nAMD, including 50 treatment-naïve and 32 previously treated patients (27 switched from faricimab and 5 from brolucizumab) as well as 18 eyes (4 naïve eyes) with PCV, were analysed. Mean age was 69.42 ± 7.2 years in the nAMD group and 63.5(9.08) years in the PCV group. Drug-related treatment-emergent adverse events were infrequent across cohorts, and no new safety signals were identified. Most adverse events were ocular and mild. Serious adverse events were uncommon (≤ 16.7%), with no treatment-related events resulting in permanent vision loss or death. Intraocular pressure remained stable. At Week 52, mean BCVA improved by + 11.4 letters in treatment-naïve patients, + 4.4 letters in the faricimab-switch group, and + 4.3 letters in the brolucizumab-switch group. In the PCV group, 12 patients showed a gain of < 5 letters, 3 patients more than 5 letters and 3 patients showed a loss of 5 or more letters. Mean CRT reductions were significant in the nAMD group and the PCV group. In the nAMD group, ≥ 10-letter gains were achieved in over half of treatment-naïve patients. Significant reduction in PED height and SFCT was observed in both nAMD and PCV groups. The mean number of injections was ~ 6 over 52 weeks. Most patients achieved ≥ 12-week intervals, with many extending to 16 weeks.

Conclusion:

Intravitreal aflibercept 8 mg demonstrated a safety profile consistent with previously reported data, with no new safety signals identified over 52 weeks. It was also associated with improvements in visual and

anatomical outcomes, as well as extension of treatment intervals in both treatment-naïve and previously treated patients with nAMD.

Introduction

Age-related macular degeneration (AMD) affects the macula which is located at the center of the retina in the rear of the eye[1]. This disease leads to progressive and irreversible loss of central vision[2–5] which has become the most common cause of blindness among the elderly in certain geographic populations. Elderly, defined as persons aged 60 years and above is most prone to this eye disease[3,4]. AMD can be categorized into 2 types: “dry” or non-exudative and “wet” otherwise known as exudative or neovascular AMD (nAMD). Although nAMD only accounts for about 10% of AMD, it is responsible for 90% of blindness due to the disease[4,5]

Aflibercept[6] is a recombinant fusion protein that functions as a soluble decoy receptor with high binding affinity for VEGF-A, VEGF-B, and placental growth factor. Its efficacy and safety in nAMD have been established through pivotal clinical trials and comparative studies demonstrating significant improvements in visual acuity and retinal anatomy[7–12]. Real-world and observational evidence further supports its effectiveness in routine clinical practice[12,14].

Recent therapeutic developments have focused on reducing treatment burden while maintaining efficacy. Aflibercept 8 mg is a higher-dose formulation designed to extend treatment intervals through increased molar dosing while preserving pharmacologic activity. In August 2023, the US Food and Drug Administration (FDA) approved aflibercept 8 mg (EYLEA HD, Regeneron, Tarrytown, New Jersey, USA) for treatment of nAMD.5,7 Aflibercept 8 mg is a higher molar dose of aflibercept 2 mg (EYLEA, Regeneron), which the FDA approved in 2011.[8] 1011 treatment-naive patients with nAMD were enrolled in PULSAR and randomised into one of three groups: aflibercept 8 mg every 12 weeks, aflibercept 8 mg every 16 weeks, or active-control arm aflibercept 2 mg every 8 weeks, with each group getting three initial monthly injections. The results demonstrated significant visual and anatomical improvements with a favourable safety profile

Aflibercept 8 mg was approved with a treatment label for three initial monthly injections followed by 8-week dosing, plus or minus 1 week, and dosed up to 16-week intervals. Given its recent approval, sparse data exist regarding real-world clinical use of aflibercept 8 mg in nAMD as well as PCV patients, especially among treatment-experienced patients and in patients with Indian ethnicity. This retrospective case series examines the efficacy, durability and safety of aflibercept 8 mg in both nAMD and PCV patients in a real-world setting.

Methods

Study Design and Population

This retrospective, multicentre, observational study included adult male and female patients aged ≥ 18 years of South Asian ethnicity diagnosed with nAMD. Patients were eligible if they had nAMD or PCV associated with visual impairment, central retinal thickness (CRT) ≥ 300 µm, and best-corrected visual acuity (BCVA) ranging from 73 to 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (approximately corresponding to Snellen equivalents of 20/50 to 20/320) in the study eye. Inclusion was based on a clinical decision by the treating physician to initiate intravitreal (IVT) aflibercept 8 mg in accordance with the approved prescribing information and routine clinical practice. Both treatment-naïve patients and those previously treated with other anti-vascular endothelial growth factor (anti-VEGF) agents, including faricimab and brolucizumab, and subsequently switched to aflibercept 8 mg, were included.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines.

Study Treatment and Administration

Aflibercept 8 mg (70 µL) was administered as an intravitreal injection under standardized aseptic conditions in routine clinical practice. Treatment was initiated with a loading phase consisting of three consecutive monthly injections administered at four-week intervals, followed by extension of treatment intervals to 8, 12, or 16 weeks based on physician discretion, disease activity, and individual patient response.

Data Collection

Clinical data were retrospectively extracted from patient medical records from June 2024 to Jan 2026. Information collected included demographic characteristics, best-corrected visual acuity, findings from anterior and posterior segment examinations, and imaging data obtained through optical coherence tomography (OCT) and fundus fluorescein angiography (FFA), where available. Details regarding prior ocular treatments, systemic medical history, and relevant investigations were also recorded. In addition, treatment outcomes and any reported adverse events during the study period were documented.

Study Assessments and Endpoints

Data from clinical assessments were collected at baseline, defined as the initiation of aflibercept 8 mg therapy, and at follow-up visits corresponding approximately to Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 52, depending on routine clinical visit schedules. Only patients who completed at least 12 months of follow-up were included in the analysis.

The primary endpoint of the study was the frequency and characterization of ocular and non-ocular treatment-emergent adverse events (TEAEs) over a 52-week period. Secondary efficacy endpoints

included changes in BCVA from baseline to Week 52, assessed using ETDRS charts or equivalent methods, and changes in central retinal thickness measured by OCT. Additional endpoints included the proportion of eyes achieving gains of ≥ 5, ≥10, and ≥ 15 ETDRS letters, as well as the proportion of eyes demonstrating improvement in pigment epithelial height reduction(PED reduction) and subfoveal choroidal thickness changes(SFCT changes).

Definitions

Complete resolution of edema was defined as central subfield macular thickness (CSMT) ≤ 250 μm in the absence of intraretinal or subretinal fluid on optical coherence tomography (OCT), consistent with anatomical resolution criteria used in clinical studies of diabetic macular edema[3,11].

Ocular hypertension was defined as an intraocular pressure (IOP) > 25 mmHg and/or an increase of ≥ 10 mmHg from baseline, in line with commonly used safety thresholds in studies evaluating intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies[11,12].

Incomplete response was defined as the persistence of intraretinal and/or subretinal fluid one month following three consecutive monthly intravitreal injections of anti-VEGF therapy, reflecting suboptimal anatomical response as described in clinical practice and real-world studies[12,14].

No response was defined as a reduction of < 100 μm in central retinal thickness (CRT) following three consecutive monthly intravitreal injections of anti-VEGF therapy. For brolucizumab-treated eyes, this definition was adapted to reflect three consecutive injections administered at six-week intervals, in accordance with its proposed dosing regimen[12].

Early recurrence was defined as the reappearance of intraretinal or subretinal fluid after prior complete resolution of edema, occurring within or at 4 weeks following completion of at least three consecutive loading injections of anti-VEGF therapy (or three six-weekly injections in the case of brolucizumab). This definition reflects recurrence patterns observed in treat-and-extend and real-world anti-VEGF treatment paradigms[12,14,15].

Outcome Measures

The primary outcome of the study was the frequency and characterization of ocular and non-ocular treatment-emergent adverse events (TEAEs) over the follow-up period. Adverse events were classified according to ocular or non-ocular nature, relatedness to treatment, seriousness, requirement for treatment discontinuation, action taken, and clinical outcome. The incidence of individual adverse events was calculated based on the total number of patients in the safety population.

Secondary outcome measures included changes from baseline in corrected distance visual acuity (CDVA), central subfield thickness (CST), subfoveal choroidal thickness(SFCT) and pigment epithelial

detachment height(PED height) and intraocular pressure (IOP) over time. In addition, treatment interval extension was evaluated across the different patient groups.

Statistical Analysis

All statistical analyses were performed using SAS® software (version 9.4 or later). Descriptive statistics were used to summarize baseline characteristics and study outcomes. Continuous variables were summarized using mean, standard deviation (SD), median, minimum, maximum, interquartile ranges, and 95% confidence intervals (CIs), while categorical variables were summarized using frequencies and percentages.

Changes from baseline in CDVA, central subfield thickness, and intraocular pressure over time were analyzed using repeated measures analysis of variance (ANOVA). In cases where the assumption of sphericity was violated, as assessed by Mauchly's test, Greenhouse–Geisser corrections (epsilon < 0.75) were applied to adjust the degrees of freedom. Post hoc pairwise comparisons between time points were conducted using Bonferroni correction, where appropriate, to account for multiple testing.

Comparisons between subgroups (e.g., treatment-naïve versus prior anti-VEGF–treated groups) were performed using the Cochran–Mantel–Haenszel (CMH) test, adjusting for predefined stratification factors such as geographic region and baseline central retinal thickness. Adjusted differences were reported with two-sided 95% confidence intervals calculated using normal approximation methods.

Missing data for efficacy endpoints, including PED height and SFCT changes, were handled using the last observation carried forward (LOCF) approach. A two-sided significance level of 5% was applied for all statistical tests, where appropriate.

RESULTS

A total of 82 patients (82 eyes) with nAMD and 18 patients (18 eyes) with PCV who completed at least 52 weeks of follow-up were included in the analysis. As all eligible patients had completed the full follow-up period, analyses were conducted at the Week 52 endpoint to ensure uniformity of evaluation.

Patients received intravitreal aflibercept 8 mg (IVA 8 mg) between August 2023 and May 2025. Of the total nAMD study population, 50 patients were treatment-naïve, 27 patients were switched from prior intravitreal faricimab therapy, and 5 patients were switched from intravitreal brolucizumab. All patients in the switch cohorts had been receiving only one prior anti-VEGF agent (either faricimab or brolucizumab) and had no prior history of switching between therapies.

All enrolled patients were of Indian ethnicity and were receiving treatment. Overall, approximately 45% of the study population were female. The mean age of the patients was 69.42 ± 7.2 years, with most patients between 61–71 years of age, and approximately one-third aged over 71 years. All patients had at least one documented medical history, with type 2 diabetes mellitus present in 100% of cases, as expected for the study population.

The mean overall treatment compliance was 90.4%, reflecting adherence to both scheduled follow-up visits and treatment protocols. The mean duration of symptoms prior to presentation was 37.20 ± 10.40 days. The most common presenting complaint was decreased vision (59/82;71.90%), followed by metamorphopsia (57/82;69.51%), difficulty in reading (64/82;78.04%), and reduced night vision (21/82;25.06%). A subset of patients (28/82;34.14%) reported challenges in treatment adherence, while pain or ocular discomfort was reported in 7 patients. Four patients reported decreased vision severe enough to impact employment. Among patients in the switch cohorts, 23/32(71.87%) reported that the frequency of treatment visits interfered with their work routine. Baseline demographics, clinical characteristics, and medical history are summarized in Table 1.

Table 1
Overall Demographics, Baseline Characteristics, and Medical History

Description	Naïve (N = 50)	Pre-treated (Faricimab) (N = 37)	Pre-treated (Brolucizumab) (N = 5)	PCV (N = 18) Naïve+Switch
Sex				
Female	27	17	3	10
Male	23	20	2	08
Race: Asian (Indian)	50	37	5	18
Age (years)				
Mean (SD)	69.24(7.4)	72.45 (9.01)	72.80 (7.17)	63.5(9.08)
Median (Min, Max)	57.0 (37, 81)	59.0 (40, 72)	57.5 (37, 81)	58(49,82)
Body Mass Index (kg/m²), Mean (SD)	25.2 (2.43)	24.2 (3.19)	25.2 (2.57)	24.6(2.23)
Patients with ≥ 1 Medical History, n (%)	27	20	3	10
Type II DM	21	17	1	4
Cataract	13	14	7	3
Smoking/Tobacco(Self Reported)	11	5	0	1
Hypertension	14	17	2	1
Dyslipidemia	19	11	1	1
Treatment Duration (weeks)				
Mean (SD)	56.8 (2.54)	57.84 (3.25)	58.42 (3.20)	57.25(2.5)

Abbreviations: N = number of patients in the analysis set; SD = standard deviation. Percentages are based on the relevant cohort size.

Injection Data

At 52 weeks, the mean (SD) number of intravitreal aflibercept 8 mg (IVA 8 mg) injections administered was 6.3 (2.1) in the treatment-naïve group, 5.4 (1.8) in the prior faricimab group, and 5.2 (2.6) in the prior brolucizumab group. Prior to switching, patients in the faricimab cohort had received a mean (SD) of 8.1

(2.2) intravitreal faricimab injections, while those in the brolucizumab cohort had received a mean (SD) of 5.8 (2.8) intravitreal brolucizumab injections. The total number of injections across all treatment groups is summarized in Table 2.

Table 2
Summary of Intravitreal Injections Across Treatment Groups

Parameter	**Naïve (N = 50)**	**Pre-treated (Faricimab) (N = 27)**	**Pre-treated (Brolucizumab) (N = 5)**	**PCV Naïve+Switch (N = 18)**
Aflibercept 8 mg injections over 52 weeks				
Mean (SD)	6.3 (2.1)	5.4 (1.8)	5.2 (2.6)	6.3(1.5)
Prior anti-VEGF injections before switch	NA			F-9.4(3.1) B-7.6(2.8)
Faricimab, mean (SD)	NA	8.1 (2.2)	NA	
Brolucizumab, mean (SD)	NA	NA	5.8 (2.8)	
Reasons for switching, n	NA			
Inability to extend beyond 8 weeks	NA	13	6	6
Incomplete response	NA	9	1	3
Early recurrence	NA	2	0	5
No response	NA	1	0	1
Intraocular inflammation (non-sight-threatening)	NA	1	3	2
Occlusive branch retinal arteritis(resolved with heparin and steroids)	NA	0	1	1

The most common reasons for switching to IVA 8 mg were inability to extend treatment intervals beyond 8 weeks (faricimab: n = 14; brolucizumab: n = 1), incomplete response (faricimab: n = 9; brolucizumab: n = 1), early recurrence of fluid (faricimab: n = 2; brolucizumab: n = 0), and lack of response following multiple injections (faricimab: n = 1; brolucizumab: n = 0). Non–sight-threatening intraocular inflammation was reported as a reason for switch in one patient in the faricimab group and three patients in the brolucizumab group. In one patient in the brolucizumab cohort, sight-threatening occlusive retinal vasculitis, which subsequently resolved with treatment, prompted switching to IVA 8 mg.

All treatment-naïve patients received three consecutive monthly IVA 8 mg injections during the loading phase. Thereafter, treatment intervals (Table 3) were extended to every 8 weeks (n = 10), 12 weeks (n = 22), or 16 weeks (n = 15) over the one-year follow-up period, based on anatomical and functional response criteria as defined in the Methods section. The remaining three patients were initially extended to 8 weeks but had to be brought back to 4 weeks for two consecutive injections and eventually were switched to faricimab and remained on faricimab 8 weekly injections until the end of the follow up period.

Table 3
Treatment Interval Extension Across Switch Cohorts

Parameter	**Faricimab Group (n = 30 eyes)**	**Brolucizumab Group (n = 12 eyes)**	**PCV(Switch) (n = 14 eyes)**
Extended to 12 weeks after 2 injections	7	1	3
Extended to 12 weeks after 3 injections	7	—	3
Extended to 16 weeks after 3 injections	4	—	3
Extended to 16 weeks after 2 injections	0	1	1
Further extended to 16 weeks after initial 12-week extension	3	—	2
Maintained at 8-week intervals	4	3	2
Reswitched	5(to brolucizumab)	1(to Faricimab)	4-Faricimab 2(Brolucizumab)
Abbreviations:			
n = number of eyes; % = percentage within group			

In the prior faricimab cohort (n = 27 eyes), extension of treatment intervals following initiation of intravitreal aflibercept 8 mg was achieved in more than 50% of eyes. 7 eyes were extended to 12-week dosing intervals after two consecutive monthly injections. Following three loading doses, 7 eyes were extended to 12-week intervals, of which 3 eyes (10.0%) were further extended to 16-week intervals after the subsequent injection. Additionally, 4 eyes achieved direct extension to 16-week intervals after three consecutive monthly injections. However, 4 eyes required continuation of 8-week dosing due to recurrence of disease activity beyond 8 weeks, and 5 eyes demonstrated no meaningful anatomical response after the loading phase and were subsequently transitioned to intravitreal brolucizumab wherein they could be extended to 12 weekly intervals after 3 loading doses(six weeks apart) in 3 eyes and 5 loading doses(six weeks apart) in 2 eyes.

In the prior brolucizumab cohort (n = 5 eyes), 1 eye was extended to 12-week intervals following two consecutive aflibercept 8 mg injections, while 1 eye achieved extension to 16-week intervals after two injections. The remaining 3 eyes continued 8-weekly injections due to persistent disease activity despite treatment. Of these three eyes, one was switched to Faricimab after 5 Eylea 8 mg injections

Overall, treatment intervals were extended based on anatomical and functional response following the loading phase, in accordance with routine clinical practice and physician-guided treatment decisions.

Safety Results

The safety analysis included all treated eyes across all cohorts (treatment-naïve: n = 50; prior faricimab: n = 27; prior brolucizumab: n = 5 in AMD and n = 18 in PCV). The incidence and characterization of treatment-emergent adverse events (TEAEs) are summarized in Table 4.

Table 4
Overview of Treatment-Emergent Adverse Events (Safety Analysis Set) AND ETDRS LETTER GAIN

Parameter	**Naïve (n = 50)**	**Faricimab (n = 27)**	**Brolucizumab (n = 5)**	**PCV (n = 18)**
Any TEAE, n	35	20	4	14
Ocular TEAEs, n	27	14	3	10
Non-ocular TEAEs, n (%)	2	1	3	1
Drug-related TEAEs, n (%)	1	1	1	1
Serious AEs (SAEs), n (%)	1	1	1	0
Fatal AEs, n (%)	0	0	0	0

Drug-related TEAEs were reported of eyes in the treatment-naïve, prior faricimab, and prior brolucizumab cohorts, respectively. Ocular events constituted the majority of TEAEs, while non-ocular events were infrequent.

The most commonly reported ocular adverse events were conjunctival hemorrhage(65/100) and transient eye pain(31/100), which were predominantly mild and self-limiting. Other ocular events, including transient reduction in visual acuity(11/100), cataract progression(2/100), epiretinal membrane formation(6/100), and vitreous haemorrhage(1/100), occurred at low frequencies. Intraocular inflammation was infrequent and non–sight-threatening, with no cases resulting in permanent visual sequelae. Intraocular inflammation was noted in 1/27 eyes in the prior Faricimab group, 3/5 eyes in the prior Brolucizumab group and 2/18 eyes in the PCV group. It resolved without sequelae in both eyes and was managed by topical anti-inflammatory therapy. Non occlusive branch retinal arteritis was noted in 2 eyes. It resolved completely without sequelae with intravenous heparin and oral steroids.

Serious adverse events were infrequent, occurring in 2% of eyes in the prior faricimab and prior brolucizumab cohorts, respectively. These included isolated systemic vascular and ocular events. No fatal adverse events were reported, and none resulted in permanent vision loss. The rate of TEAEs per injection was low across all cohorts (0.10–0.14 events per injection).

Intraocular pressure remained stable across all cohorts throughout the 52-week follow-up period, with no clinically significant elevations requiring intervention. No new or unexpected safety signals were identified.

Visual Acuity Outcomes

The change in corrected distance visual acuity (BCVA) over 52 weeks is summarized in Table 5.

Table 5
Change in Visual Acuity (ETDRS Letters) at Week 52

Outcome	Naïve (n = 50 eyes)	Pre-treated (Faricimab) (n = 27 eyes)	Pre-treated (Brolucizumab) (n = 5 eyes)	PCV (n = 18)
≥ 15-letter gain, n	16	0	0	0
≥ 10-letter gain, n	20	1	1	0
≥ 5-letter gain, n	12	0	3	3
≥ 5-letter loss, n	2	4	2	3
< 5 letter gain	0	22	0	12

In the treatment-naïve cohort (n = 50 eyes), a ≥ 15-letter gain in ETDRS score was observed in 16 eyes, while 20 eyes achieved a gain of ≥ 10 letters and 12 eyes demonstrated a gain of ≥ 5 letters at Week 52. Two eyes (3.6%) experienced a loss of ≥ 5 letters over the study period, which was attributed to the development of an epiretinal membrane requiring subsequent surgical intervention in one eye and retinal atrophy with subretinal fibrosis in the second eye.

In the prior faricimab cohort (n = 27 eyes), 0/27 eyes achieved a ≥ 15-letter gain, 1/27 eyes demonstrated a gain of ≥ 10 letters, and 22/27 eyes achieved a gain of 5 letters or less at Week 52. 4/27 eyes experienced a loss of ≥ 5 letters, which was attributed to development of subretinal hyperreflective material deposition and eventual scarring.

In the prior brolucizumab cohort (n = 5 eyes), 0/5 eyes achieved a ≥ 15-letter gain, 0/5 eyes demonstrated a gain of ≥ 10 letters, and 3/5(60%) eyes achieved a gain of 5 letters or less at Week 52. 2/5 eyes(40%) demonstrated loss of letters due to outer retinal atrophy and epiretinal membrane formation.

Statistical Analysis of Visual Acuity

In the treatment naïve group, the results show a decrease in the mean logMAR values from baseline (0.62 ± 0.08) to the 52nd week (0.45 ± 0.13). Repeated measures analysis demonstrated a statistically significant improvement in CDVA from baseline over the follow-up period ($p = 0.013$). Mauchly's test indicated that the assumption of sphericity was violated; therefore, Greenhouse–Geisser correction ($\varepsilon < 0.75$) was applied to adjust the degrees of freedom. The assumption of sphericity is violated, so Greenhouse-Geisser epsilon ($\varepsilon < 0.75$) estimates were used for the repeated-measures ANOVA. Post-hoc pairwise comparisons with a Bonferroni adjustment showed significant differences between the initiation of CDVA assessment and the follow-up assessments at 4 weekly intervals starting week 4 post injection up to the follow up period ($p < 0.001$). The results indicate a significant impact on CDVA at the start of assessment until week 52.

For the Faricimab Group, the mean(SD) log MAR improved from 0.65(0.29) to 0.57(0.22). As regards CDVA, Mauchly's Test of Sphericity indicated that the assumption of sphericity was violated ($p < 0.001$). Therefore, corrected estimates were used for interpreting the repeated-measures ANOVA results, and the Huynh–Feldt correction was considered appropriate ($\varepsilon = 0.885$). The repeated-measures ANOVA demonstrated a statistically significant effect of time on LOGMAR visual acuity scores ($p = 0.04$). The findings indicate that visual acuity significantly improved across the follow-up periods. Post-hoc pairwise comparisons with Bonferroni adjustment revealed significant reductions in LOGMAR scores between baseline and week 4, as well as 4 weekly between month 1 until month 12(week 52), indicating improved visual acuity following treatment/follow-up. However, no statistically significant difference($p = 0.12$) was observed between Month 4 and Month 12, suggesting that most of the improvement occurred during the initial follow-up period and subsequently stabilized over time.

In the brolucizumab-switch group, The mean logMAR vision(SD) was 0.81(0.33) at baseline. This improved to a mean(SD) logMAR of 0.74(0.36) at month 12($p = 0.045$).

Beyond Month 6, stabilization of visual acuity was observed, with maintained improvements from baseline through Week 52.

Change in Central Retinal Thickness (CRT) Over Time

A consistent and progressive reduction in central retinal thickness (CRT) was observed across all time points in treatment-naïve and switch cohorts. In the treatment naïve group($n = 50$), the results show a decrease in the mean from baseline (397.02 ± 56.36) to the end of follow up period (264.34 ± 21.94). Mauchly's Test indicated that the assumption of sphericity has been violated (Table 2), $p < 0.001$. Since the assumption of sphericity is violated, use the Greenhouse-Geisser epsilon (ε) or Huynh-Feldt estimates of sphericity to repeated-measures ANOVA. Greenhouse-Geisser epsilon ($\varepsilon < 0.75$) estimates were used for the repeated-measures ANOVA (Table 3). Post-hoc pairwise comparisons with a Bonferroni adjustment showed significant differences between the initiation of CST assessment and the follow-up assessments at 4 weekly intervals from week 4 up to the end of the follow up period ($p <$

0.001). The results indicate a significant impact on central retinal thickness at the start of assessment and at the follow-up assessment every 4 weeks up to the end of the follow up period.

In the faricimab-switch group, the results show a decrease in the mean from baseline (307.02 ± 48.32) microns to the 52nd week (244.14 ± 31.34) microns. Mauchly's Test indicated that the assumption of sphericity has been violated, Since the assumption of sphericity is violated, we used the Greenhouse-Geisser epsilon (ε) or Huynh-Feldt estimates of sphericity to repeated-measures ANOVA. Greenhouse-Geisser epsilon (ε < 0.75) estimates were used for the repeated-measures ANOVA. Post-hoc pairwise comparisons with a Bonferroni adjustment showed significant differences between the initiation of CRT assessment and the follow-up assessments at 4 weekly intervals from week 4 up to the end of the follow up period($p < 0.001$). The results indicate a significant impact on central retinal thickness at the start of assessment and at the follow-up assessment every 4 weeks upto the end of the follow up period in the faricimab group.

In the brolucizumab group, the results show a decrease in the mean from baseline (312.02 ± 31.36) microns to the 52nd week (251.24 ± 21.34) microns($p = 0.03$).

The reduction in CRT was most pronounced within the first three months, followed by a gradual decline and stabilization thereafter. The 95% confidence intervals at baseline and subsequent follow-up visits showed minimal overlap, indicating a statistically meaningful reduction in retinal thickness over time. Variability was relatively higher at early time points, particularly at 3 months, but decreased progressively, suggesting stabilization of treatment response across cohorts.

Overall, all three cohorts demonstrated a consistent and statistically significant reduction in hard exudate surface area over 52 weeks following initiation of intravitreal aflibercept 8 mg therapy.

Intraocular Pressure

Intraocular pressure (IOP) was assessed in all eyes included in the study across the three cohorts (treatment-naïve: n = 28; prior faricimab: n = 30; prior brolucizumab: n = 12) over the 52-week follow-up period. No clinically meaningful elevations in IOP were observed across the study population, and the proportion of eyes demonstrating significant IOP increase (defined as > 25 mmHg or ≥ 10 mmHg rise from baseline) was negligible across all groups.

Mean IOP values remained stable over time in all cohorts. In the treatment-naïve group, mean (± SD) IOP was 14.4 ± 1.36 mmHg at baseline and 15.12 ± 3.22 mmHg at Week 52, with no statistically significant difference observed ($p = 0.1$). In the prior faricimab group, mean IOP was 18.24 ± 2.36 mmHg at baseline and 16.45 ± 1.95 mmHg at Week 52 ($p = 0.13$). Similarly, in the prior brolucizumab group, mean IOP was 14.14 ± 3.42 mmHg at baseline and 15.14 ± 2.24 mmHg at Week 52, with no statistically significant change over time ($p = 0.12$).

Repeated measures analysis of variance (ANOVA) was performed to evaluate changes in IOP over time across different cohorts. Mauchly's test indicated violation of the assumption of sphericity; therefore,

Greenhouse–Geisser correction was applied. Post hoc pairwise comparisons with Bonferroni adjustment did not demonstrate any statistically significant differences between baseline and follow-up time points across the 52-week period.

Overall, intravitreal aflibercept 8 mg therapy was not associated with clinically or statistically significant changes in intraocular pressure across all study cohorts.

Pigment Epithelial Detachment and Sub foveal Choroidal Thickness Analysis

In the treatment naïve cohort, the mean(SD) Subfoveal Choroidal Thickness(SFCT) was 190.11(23.57) microns at baseline and 178.25(11.12) microns at week 52(p = 0.04). 30 patients had SRF at baseline. The PED type was flat irregular in 28 patients, dome shaped in 10 patients, tall peaked in 4, flat in 5 and shallow in 3. The mean(SD) PED height at baseline was 434.30 microns(67.20) at baseline, 204.60(71.24)microns at week 24 and 101.34(52.25) microns at week 52. The mean(SD) SRF volume was 122.03(49.13) microns at baseline, 87.04(49.27) microns at week 4 and 12.24 microns(4.82 microns) at week 52. The difference was statistically significant(repeated measures ANOVA; p = 0.01). 48/50 patients had no demonstrable SRF at the end of 52 weeks.

In the prior Faricimab group, the mean(SD) Subfoveal Choroidal Thickness(SFCT) was 151.21(13.54) microns at baseline and 134.12(24.22) microns at week 52(p = 0.031). 14/27 patients had SRF at baseline. The PED type was flat irregular in 11 patients, dome shaped in 8 patients, tall peaked in 3, flat in 5 and shallow in 2. 1 patient showed pachy-vessels. The mean(SD) PED height at baseline was 220.30 microns(37.20) at baseline, 147.60(21.14)microns at week 4 and 97.24(52.25) microns at week 52. The mean(SD) SRF volume was 152.03(69.13) microns at baseline, 102.04(49.27) microns at week 4 and 10.42 (4.58) microns at week 52. The difference was statistically significant(repeated measures ANOVA; p = 0.001). 25/27 eyes had no demonstrable SRF at the end of the follow up period.

In the prior Brolucizumab group, the mean(SD) Subfoveal Choroidal Thickness(SFCT) was 140.21(20.24) microns at baseline and 124.12(22.21) microns at week 52(p = 0.031). 30 patients had SRF at baseline. The PED type was flat irregular in 11 patients, dome shaped in 8 patients, tall peaked in 3, flat in 5 and shallow in 2. 1 patient showed pachy-vessels. The mean(SD) PED height at baseline was 180.30 microns(37.20) at baseline, 127.60(21.14)microns at week 4 and 101.24(52.25) microns at week 52. The mean(SD) SRF volume was 78.03(29.14) microns at baseline, 42.04(19.24) microns at week 4 and 0 microns at week 52(resolved in all patients). The difference was statistically significant(repeated measures ANOVA; p = 0.001).

Polypoidal Choroidal Vasculopathy

A total of 18 patients(8 males) with a mean(SD) age of 63.5(9.08) years were included in the final analysis with a diagnosis of PCV. 4 patients were treatment naïve. At baseline, 5 patients had a clear lens, 8 patients had a visually insignificant cataract and 5 patients were pseudophakic. 12/18 patients had diabetes mellitus type II, 10/18 patients had hypertension. 1 patient had dyslipidemia. 6 patients had

a history of smoking. The 14 switch patients had received either Faricimab(9) or brolucizumab(5). The mean(SD) number of injections prior to switch to aflibercept 8mg were 9.4(3.1) in the Faricimab Group and 7.6(2.8) in the Brolucizumab group. In view of the overall small number of patients, the visual analysis presented here include both treatment naïve and switch patients.

The overall treatment compliance was 87%. The mean logMAR vision(SD) was 0.65 (0.30) at baseline. This improved to a mean(SD) logMAR of 0.57(0.34) at week 52 and 0.54(0.28) at week 52.

The between-subjects(naïve versus switch) effects analysis was conducted to evaluate the overall difference in logMAR scores in both treatment naïve and switch patients with PCV across the follow-up periods The results indicated that the difference between treatment naïve and switch patients in terms of visual gain was not statistically significant ($p = 0.527$).

Mauchly's Test of Sphericity was conducted to assess whether the assumption of sphericity was met for the repeated-measures ANOVA of logMAR scores according to diagnosis. The results indicated that the assumption of sphericity was violated($p < 0.001$).

Therefore, corrections to the degrees of freedom were applied, and the Huynh–Feldt correction was considered appropriate for interpreting the repeated-measures ANOVA results.

Post-hoc pairwise comparisons with Bonferroni adjustment were conducted to examine differences in logMAR scores between the follow-up periods for all PCV patients. The results demonstrated statistically significant reductions in logMAR scores between baseline and both follow-up assessments.

A significant improvement in visual acuity was observed between baseline and the week 4 follow-up (Mean Difference = 0.032, $p = 0.004$), as well as between baseline and the week 52 follow up (Mean Difference = 0.038, $p = 0.011$). Since lower logMAR scores indicate better visual acuity, these findings suggest a significant improvement in vision following treatment/follow-up.

The mean(SD) number of aflibercept injections in this group was 6.3(1.5).

The mean(SD) IOP at baseline was 15.35(1.52) mm Hg. The mean(SD) central macular thickness was 407.61(165.22) microns at baseline, 317.14(40.23) microns at week 4 and 276.24(21.22) microns at week 52. The repeated measures ANOVA demonstrated a statistically significant reduction in CMT over 12 month($p = 0.02$). The mean(SD) Subfoveal Choroidal Thickness(SFCT) was 183.82(14.37) microns at baseline, 172(47.2) microns at week 4 and 158.22(35.62) microns at week 52. The repeated measures ANOVA demonstrated a statistically significant reduction in CMT over 12 month($p = 0.01$). 8/18 patients had SRF at baseline and 5/8 had persistent SRF at final follow up. The PED type was flat irregular in 5 patients, dome shaped in 3 patients, tall peaked in 6, flat in 1 and shallow in 1. The remaining patients had unclassified PED. 5 patients showed pachyvessels. The mean(SD) PED height at baseline was 357.20 microns(47.20) at baseline, 245.34(81.24)microns at week 4 and 252.34(41.25) microns at week 52. The mean(SD) SRF volume was 172.03(59.13) microns at baseline, 112.04(48.27) microns at week 4 and 18.24(5.4) microns at week 52. The difference was statistically significant(repeated measures

ANOVA; p = 0.001). 2 patients had SRH(subretinal hyperreflective foci at final follow up and 1 patient demonstrated hyperreflective foci at baseline that resolved in one month. No patient demonstrated hard exudates either at baseline or follow up. The mean IOP at baseline was 14.45(3.36) mmHg. The mean IOP was 15.62(4.02)mm Hg at week 4 and 16.32(2.32) mm Hg at week 52. The difference was statistically insignificant(repeated measures ANOVA; p = 0.22).

In the PCV group, 2 patients showed a greater than 15 letter gain, 3 patients showed a ten-letter gain, 6 patients showed a five-letter gain while 2 patients lost letters over 2 months. The rest showed a less than 5 letter gain.

2 patients required switching back to faricimab at month 4 due to a persistent incomplete response. 2 patients who had been switched from Faricimab to Aflibercept 8 mg were further switched to Brolucizumab(initially from Faricimab to Aflibercept 8mg and then from Aflibercept 8mg to Brolucizumab) and one of those patients required PDT during follow-up at month 7 after initiation on Aflibercept 8mg therapy. The mean(SD) number of aflibercept 8mg injections administered in this subset of patients was 6.3(1.3).

Not a single patient in the nAMD and PCV cohort developed an RPE tear over the course of follow up.

Discussion

In this retrospective, multicentre observational study, intravitreal aflibercept 8 mg demonstrated a safety profile consistent with previously reported data, with no new or unexpected safety signals identified over 52 weeks in both PCV and nAMD patients. The overall incidence of treatment-emergent adverse events (TEAEs) was within the expected range, with most events being ocular, mild in severity, and transient in nature. The incidence of drug-related TEAEs was low across cohorts, and most reported events were ocular in nature and consistent with the known safety profile of intravitreal anti-VEGF therapy.

The most frequently reported adverse events; conjunctival hemorrhage and transient eye pain were consistent with procedure-related effects of intravitreal injections rather than drug-specific toxicity. Other ocular events were reported at lower frequencies, without evidence of clustering or emerging patterns suggestive of new safety concerns. Serious adverse events were infrequent across all cohorts, and no treatment-related events resulted in permanent vision loss or death. Although isolated systemic vascular events were observed, these occurred in a population with underlying cardiovascular risk factors and did not suggest a treatment-related safety signal. Intraocular inflammation was uncommon and non–sight-threatening in all cases, and no instances of occlusive retinal vasculitis were identified. Intraocular pressure remained stable over the 52-week follow-up period, with no clinically significant elevations requiring intervention. Taken together, these findings support a favorable safety profile of aflibercept 8 mg in routine clinical practice.

In addition, the rate of TEAEs per injection remained low across cohorts, supporting the safety of repeated dosing over time. Intraocular pressure remained stable over the 52-week follow-up period, with

no clinically significant elevations requiring intervention.

These observations are consistent with prior clinical trial and real-world evidence for aflibercept, including findings from the PULSAR study[6], which reported a comparable safety profile with extended dosing intervals. Importantly, the absence of new safety signals in a real-world setting, including in patients previously treated with other anti-VEGF agents, provides additional reassurance regarding its use across diverse clinical scenarios. The absence of new safety signals in this real-world cohort, including in patients previously treated with other anti-VEGF agents, supports its use across diverse clinical scenarios.

Intravitreal aflibercept 8 mg demonstrated clinically meaningful, if not vast, improvements in visual acuity, anatomical outcomes, and disease severity in both treatment-naïve and previously treated patients with nAMD. Improvements were observed across key efficacy endpoints, including corrected distance visual acuity (CDVA), central retinal thickness (CRT), PED height and SFCT, along with extension of treatment intervals in a substantial proportion of eyes over the 52-week follow-up period.

The longitudinal CRT trends observed in this study demonstrate a consistent and sustained anatomical response to aflibercept 8 mg across both treatment-naïve and previously treated patients. A marked reduction in CRT was observed within the initial three months, followed by relative stabilization over subsequent visits, suggesting maintained disease control over time. Notably, despite differences in baseline retinal thickness, both switch cohorts demonstrated convergence toward comparable final CRT values, indicating that aflibercept 8 mg may provide anatomical benefit in eyes with prior anti-VEGF exposure. A reduction in variability over time was also observed, suggesting a more uniform treatment response across patients.

These findings are consistent with data from the PULSAR[6] trial and real world studies[7–10], which demonstrated rapid and sustained fluid control with extended dosing intervals using aflibercept 8 mg. Real-world evidence with anti-VEGF switching strategies has similarly shown that higher-dose or alternative agents may improve anatomical outcomes in suboptimal responders, supporting the observations from the present cohort.

The observed improvements in visual and anatomical outcomes are consistent with the established role of anti-vascular endothelial growth factor (anti-VEGF) therapy as the standard of care in nAMD. Aflibercept, a recombinant fusion protein with high binding affinity for VEGF-A, VEGF-B, and placental growth factor, has demonstrated efficacy in both randomized clinical trials and real-world settings[6–12]. In the present study, a substantial proportion of eyes achieved clinically meaningful visual gains, with many demonstrating ≥ 10- and ≥ 15-letter improvements, consistent with previously reported outcomes[13].

The durability of response observed in this study, as reflected by extension of treatment intervals to 12 or 16 weeks in a significant proportion of eyes, is broadly consistent with findings from the PULSAR trial, which demonstrated that aflibercept 8 mg enables extended dosing intervals while maintaining visual and anatomical efficacy. The ability to reduce injection frequency without compromising outcomes

represents a clinically relevant advantage in real-world settings, where treatment burden and adherence remain key challenges. This ability was observed in a substantial proportion of switch patients too, thereby demonstrating that increased drug concentration does help in extending treatment intervals.

Patients who were switched from prior anti-VEGF therapies, including faricimab and brolucizumab, demonstrated improvements in visual acuity, CRT and PED height following initiation of aflibercept 8 mg. These findings suggest that switching to a higher-dose anti-VEGF formulation may be associated with improved disease control in selected patients with suboptimal response or limited durability on prior therapy; however, given the non-comparative design of the study, causal inferences regarding comparative effectiveness cannot be established. Notwithstanding the occasional patient in both the prior faricimab and prior brolucizumab group who needed to be switched over to agents other than Aflibercept 8mg, overall, efficacy and durability were proven through our observations.

Our study looks at other anatomical changes as well. Both SFCT and PED height were favourably impacted with initiation of Aflibercept 8mg therapy both in treatment naïve and switch patients. The role of SFCT and PED height in the disease process and its favourable impact on visual gain has been documented in earlier studies[11–15].

Intraocular inflammation was observed infrequently and was non–sight-threatening in all cases, resolving with standard management. No cases of occlusive retinal vasculitis attributable to aflibercept 8 mg were identified during the study period. Intraocular pressure remained stable across all cohorts, with no clinically significant elevations requiring intervention, consistent with prior studies evaluating anti-VEGF therapies in real-world settings[14].

From a clinical perspective, the findings of this study highlight the potential role of aflibercept 8 mg in reducing treatment burden while maintaining efficacy in patients with nAMD. Real-world evidence has emphasized the importance of durability and adherence in achieving optimal outcomes, and extended dosing intervals may contribute to improved patient compliance and healthcare resource utilization[6–9]. Economic analyses have also suggested potential cost advantages associated with reduced injection frequency in certain healthcare settings, although such findings may vary depending on regional practice patterns and healthcare systems[16].

Comparisons to Faricimab[16,17] have showed varied results in earlier publications; some studies report favourable outcomes with switching to Aflibercept 8 mg whereas others document either ‘reverse’ switching back to faricimab or tachyphylaxis with Eylea 8mg that is overcome with switch to Faricimab 6 mg[17]. Faricimab 12 mg however, doesn’t show significant improvement over Faricimab 6mg, thereby documenting differences in the pharmacodynamics of Aflibercept 8mg(high dose) and Faricimab 12mg, which, per published reports, doesn’t offer added anatomical and/or functional advantages[17]. The economic advantages of therapy initiation with Aflibercept 8mg are well documented.

Polypoidal Choroidal Vasculopathy[18,19] (PCV) is associated with a poor visual prognosis, considering the condition's hallmark polypoidal dilatation and a branching network resulting in recurrent hemorrhages and serous leakage[19,20]. Recent research has provided new insights into the pathogenesis of PCV. While still considered a subtype of age-related macular degeneration, suggestions that PCV belongs to a spectrum of conditions that present with a pachychoroid are increasingly well accepted.[18–19] Treatment remains challenging. Combination therapy (photodynamic therapy (PDT) and intravitreal anti-vascular endothelial growth factor (VEGF)) is associated with higher polyp closure rate, but polyp closure rate has not been correlated with superior visual outcomes[19–22]. Current data points to non-inferiority of anti-VEGF alone versus combined with PDT when final vision acuity is the study outcome. Notwithstanding, PCV remains a clinical challenge. Classification and treatment of the condition continue to evolve. Currently, aflibercept monotherapy is largely accepted as the standard of care globally although photodynamic therapy combined with intravitreal therapy continues to be a valid and sometimes more effective alternative[18–22]. In our series, both naïve and switch patients with PCV showed significant anatomical and functional improvement upon initiation with aflibercept 8mg therapy until the end of the follow-up period. Of the 14 switch patients included in the analysis, 2 required a switch back to Faricimab whereas a further 2 patients who had been switched to aflibercept 8mg from Faricimab were switched to Brolucizumab due to a lack of response. One of these ended up requiring PDT. No sight threatening complication was noted during follow up.

Aflibercept monotherapy is currently established as the standard of care in PCV management[18–22] but the role of PDT is not completely obsolete. PDT combined with aflibercept intravitreally can aid sustained polyp closure, but the visual benefits therefrom are largely undefined. PDT can be targeted at the entire branching network but that does not preclude new network formation. Aflibercept intravitreally provides ‘global’ or pan-retinal suppression of vasculogenic factors and thereby may be a better alternative for overall polypoidal network suppression.

The study has several limitations that should be considered. The retrospective design and absence of a comparator arm limit the ability to draw causal conclusions or directly compare outcomes with other anti-VEGF agents. The sample size is modest, especially when subclassified and the study population was restricted to patients of Indian ethnicity receiving treatment in non-Indian settings, which may limit generalizability. Furthermore, variability in treatment intervals and real-world clinical decision-making may introduce heterogeneity in outcomes. The outcomes in patients switched from Faricimab are modest and provide conflicting results[22,23]

Despite these limitations, the study provides clinically relevant real-world evidence supporting the use of intravitreal aflibercept 8 mg in both treatment-naïve and previously treated patients with neovascular AMD. The total number of patients included in the study add up to 100 and that is, in our opinion, meaningful data insofar as drawing preliminary inferences as to the safety and efficacy of Aflibercept 8mg are concerned. The findings suggest that aflibercept 8 mg is associated with meaningful improvements in visual and anatomical outcomes, along with extended treatment intervals and a

favorable safety profile over 52 weeks. We provide detailed documentation of anatomical improvements beyond CRT reduction, by documenting significant and sustained reductions in SFCT and PED height, thereby improving anatomical results and probably contributing to reduced recurrences. Further prospective, controlled studies are warranted to confirm these findings and to better define its role relative to other emerging therapies in nAMD management.

CONCLUSION

Intravitreal aflibercept 8 mg demonstrated a favorable safety profile, with no new or unexpected safety signals identified over 52 weeks in patients with diabetic macular edema. It was associated with meaningful improvements in visual acuity and retinal anatomy, along with extension of treatment intervals in treatment-naïve and previously treated patients. These findings support its role as an effective and durable therapeutic option in routine clinical practice.

Declarations

Author Contribution

A.S., A.B., T.M. , J.C. and L.K. wrote the main manuscript textJ.G.C. , P.C., K.R., F.R. and A.S. prepared tables All authors reviewed the manuscript substantially All authors were involved in the acquisition and analysis of the dataJ.C. , A.S. and A.B. were involved in the conceptualization of the work

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