

Short-Term Treatment Outcomes of Brolucizumab in Patients with Neovascular Age-Related Macular Degeneration: A Multicentre Indian Real-World Evidence Study

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Objective: To evaluate the short-term effectiveness and safety outcomes following brolucizumab treatment in patients with neovascular age-related macular degeneration (nAMD) as a part of real-world clinical practice in India.

Methods: This was a retrospective, observational, multicentre study including patients (≥ 50 years old) diagnosed with nAMD. Anonymized data of the patients receiving the first dose of brolucizumab intravitreal injection (IVI) who were either treatment-naïve or previously treated with a single or a combination of other anti-VEGF IVIs were included. The present study reported the change in retinal fluid levels from baseline to month 3, best-corrected visual acuity (BCVA), central retinal thickness (CRT), and the number of injections received. The adverse events in the three months after brolucizumab treatment initiation were also monitored.

Results: The study included 63 patients (65 eyes) from four study centres across India (mean age: 69.1 ± 9.7 years). A total of 82 brolucizumab injections were administered during the 3 months of study duration, with 52/65 (80.0%) eyes receiving only 1 injection. Resolution of IRF, SRF, and PED was observed in 76.9%, 64.6%, and 67.7% of eyes, respectively. Further, a significant reduction in CRT was observed (baseline: $403.5 \pm 118.7 \mu\text{m}$; month 3: $308.3 \pm 73.8 \mu\text{m}$; $p < 0.001$), and BCVA also improved notably from 0.7 ± 0.5 logMAR at baseline to 0.5 ± 0.4 logMAR at month 3 ($p < 0.001$). Adverse events (AEs) were reported in 3 eyes from 3 patients; retinal pigment epithelial rip (1) and subretinal hemorrhage (2) after the first injection of brolucizumab, however, none discontinued the treatment.

Conclusion: The study reports on the short-term effectiveness and tolerability of brolucizumab therapy in the management of nAMD in both treatment-naïve and switch eyes. Brolucizumab was observed to have a favourable benefit-risk profile, and study results were within the known safety profile, with no instances of intraocular inflammation.

Keywords: anti-VEGF, brolucizumab, nAMD, real-world evidence, India

Introduction

Age-related macular degeneration (AMD) is one of the major causes of irreversible central visual impairment and is responsible for 8.7% of all cases of blindness worldwide.¹⁻⁴ Globally, the number is estimated to rise to nearly 300 million by the year 2040.⁵ In India, early AMD and the resulting vision loss are a growing concern, with reports of a prevalence ranging from 1.4% to 3.1%, and age is found to be affecting the prevalence.⁶ The wet or neovascular AMD (nAMD), though less frequent, has been associated with 90% of cases of acute blindness.⁷⁻⁹

The main objectives of nAMD treatment are to prevent the formation of new blood vessels (macular neovascularization) and to improve and stabilize vision through fluid reduction.¹⁰⁻¹³ The anti-vascular endothelial growth factor (anti-VEGF) agents are gold standards for the management of nAMD.^{11,12} The commonly used anti-VEGFs, bevacizumab (off-label), ranibizumab, and

afibercept have resulted in significant improvement in visual function and thus ameliorate the quality of life of the affected patients. However, some patients may require repeated intravitreal injection (IVI) administration of monthly anti-VEGF injections for a longer duration. This reduces patients' compliance with the treatment, leading to decreased monitoring and poor visual outcomes, which further imposes a significant burden on patients, caregivers, and treating physicians.^{14,15} As per the American Society of Retina Specialists (ASRS) preference and trends (PAT) survey, the physicians have identified a significant unmet need in the management of nAMD due to the frequent injections required for treatment and further expressed a need for more effective treatment with longer intervals between injections.¹⁶

Brolucizumab, a humanized, single-chain variable fragment antibody that inhibits VEGF-A,¹⁷ is the latest addition to the armamentarium of anti-VEGF agents, approved (in October 2019) by the United States Food and Drug Administration (US FDA) and by the Drugs Controller General of India (DCGI) in July 2020.¹⁸ With a molecular mass of approximately 26 kDa, brolucizumab readily penetrates the retina resulting in greater efficacy and longer durability of the effect than other anti-VEGF agents. Additionally, it exhibits rapid systemic clearance and minimal systemic exposure.^{19,20} The results of two large Phase III, multicentre, randomized clinical trials, HAWK and HARRIER, have established the efficacy and safety of brolucizumab in the treatment of nAMD.^{21,22} The once-every-12 weeks (q12w) regimen of the drug provides adequate treatment outcomes while reducing the number of IVIs required for patients with nAMD.¹⁷ In a post hoc analysis of the HAWK and HARRIER studies performed by the safety review committee (SRC), an overall incidence of intraocular inflammation (IOI) was 4.6% with brolucizumab, 3.3% for IOI with retinal vasculitis (RV) and 2.1% for IOI with RV and retinal vascular occlusion. The overall incidence of moderate visual acuity loss associated with IOI was <1%.^{23,24} Also, in a network meta-analysis conducted by Finger et al,²⁵ it was observed that among all anti-VEGF treatments, brolucizumab showed better reduction in retinal thickness, comparable BCVA gains and discontinuation rates, with lesser number of injections compared to other anti-VEGF agents.

Currently, there are very limited data available on the effectiveness and safety of brolucizumab in the real-world patient population in India. The available literature evidence is restricted to either other countries or a specific institute in India with limited patient follow-up data.^{26–30} These findings are, therefore, difficult to extrapolate to the Indian population due to differences in the demographics, ethnicity, and clinical presentations.

In order to address the gap in the literature, the present study was designed to understand the effectiveness and safety of brolucizumab in real-world clinical practice in a broader Indian nAMD population, and how it differs in practice from other countries or prescription as per label.

Methods

Study Design

This retrospective, observational, multicentre study included all patient eyes treated with brolucizumab in the 6 months period from 4 sites across India viz. Dr. Milan's Retina Care Centre, Rajkot (Gujarat), Disha Eye Hospital, Kolkata (West Bengal), Susrut Eye Foundation and Research Centre, Kolkata (West Bengal), and Narayana Nethralaya, Bangalore (Karnataka). Data were collected from the Electronic Medical Records (EMRs) database of the study sites, and patients' confidentiality was maintained using anonymized and de-identified data at the source level. A grader specific to each individual centre performed the OCT evaluation. The grader was masked for the details of the study and diagnosis.

This study complied with the tenets of the Declaration of Helsinki and was approved by an Independent Ethics Committee (IEC), Royal Pune Independent Ethics Committee, India (Regn Number: ECR/45/Indt/MH/2013/RR-19) for Dr. Milan's Retina Care Centre, Rajkot, India, along with Institutional Review Boards (IRBs) at Susrut Eye Foundation and Research Centre, Kolkata, India (Regn Number: ECR/408/Inst/WB/2013/RR-20); Disha Eye Hospitals, Kolkata, India (Regn Number: ECR/846/Inst/WB/2016/RR-19); and Narayana Nethralaya, Bangalore, India (Regn Number: ECR/187/Inst/Kar/2013/RR-19). Informed consent waiver was obtained from IEC and IRBs considering the risk of this research was not greater than minimal risk and the waiver would not adversely affect the rights and welfare of study participants. This study was registered in the Clinical Trial Registry of India (CTRI/2021/11/037815).

Study Population

Patients (male or female) aged ≥ 50 years treated with brolucizumab IVI [first dose during the index period (01 October 2020 to 31 March 2021)] for nAMD were included in the study. They were either treatment-naïve or previously treated with a single or a combination of other anti-VEGF IVIs. Recalcitrant cases were defined as eyes with fluid on the spectral-domain OCT, which was either worsening or persistent ($<100\mu\text{m}$ reduction) despite repeated consecutive doses of aflibercept, ranibizumab or bevacizumab injections. Patients were required to have records of VA and optical coherence tomography (OCT) assessments at baseline and month 3 after initiating treatment with brolucizumab. The decisions whether to administer loading doses, the frequency of monitoring visits and of injections were solely at the discretion of the treating clinician. The retreatment criteria included drop of one or more lines in the Snellen's visual acuity chart; an increase in OCT CRT of at least $100\mu\text{m}$; worsening of existing fluid (intraretinal fluid [IRF] or subretinal fluid [SRF]); or appearance of new fluid (PED/SRF/IRF); or new location of CNVM as compared to the previous visit; or evidence of persistent fluid on OCT 1 month after the previous injection.³¹ For polypoidal choroidal vasculopathy (PCV) cases, diagnosis was confirmed based on standard SD OCT criteria, fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA).³²

Patients with dry AMD, geographic atrophy, and other retinal diseases in the eyes were excluded besides those who were undergoing additional ocular treatment along with anti-VEGF agents for nAMD.

Outcome Assessments

The primary endpoint of the study was to evaluate the short-term effectiveness of brolucizumab on fluid levels [absence/reduction of IRF, SRF, and pigment epithelial detachment (PED)] in treatment eyes ($n = 65$) at month 3 compared to the baseline. The secondary endpoint measures included changes in visual outcome in terms of mean change in the best-corrected visual acuity (BCVA) from baseline to month 3 as measured by logarithm of the minimum angle of resolution (logMAR; measurement by Snellen chart converted to logMAR for analysis), the evaluation of the effectiveness of brolucizumab on fluid levels (IRF, SRF, PED) from baseline to months 1 and 2, and change in the CRT as assessed by OCT from baseline to months 1, 2, and 3. Further, the number of anti-VEGF injections, non-injection visits (monitoring visits), and the total number of patient visits during the first 3 months of treatment with brolucizumab were recorded. The ocular and non-ocular safety of brolucizumab was determined by capturing the incidence and characteristics of treatment-emergent adverse events (AEs) at each visit. The exploratory endpoint was to assess whether the improvements observed at month 3 were sustained at month 6.

Statistical Analysis

Assuming that up to 81% of patients' eyes would be fluid-free at month 3 (as observed in HAWK and HARRIER clinical trials), with a power of 80%, a sample size of approximately 44 patients' eyes was considered enough for this real-world study.

As this was a descriptive study, no comparative analysis was conducted. Descriptive statistics were tabulated for the demographic and clinical characteristics as well as outcome variables. Continuous variables were summarized as the number of observations, means, and standard deviations (SD). On the other hand, categorical variables were summarized as counts and proportions (overall number of injections, the total number of visits, the number of non-injection visits, etc.). For continuous data, the changes from baseline to the follow-up period were assessed using the Wilcoxon-signed rank test. Likewise, for categorical data, the changes from the baseline to the follow-up period were assessed using the Chi-square test. A p-value of <0.05 was considered statistically significant. No missing value imputation was performed. The analyses were conducted separately for the study eyes (patients) with 1, 2, and 3 months of follow-up from the index date (first injection of brolucizumab). A window period of ± 15 days was considered during the entire study period. All calculations were performed using R language (version 4.2.2) with R studio software (version 1.4.1106) and Microsoft Excel version 2021.

Results

A total of 76 patients were screened, of which 63 patients met the selection criteria [65 eyes {oculus dexter (OD) = 27, oculus sinister (OS) = 34 and oculus uterque (OU) = 4}] and were included in the study (Figure 1). Of these, 25 (38.5%)

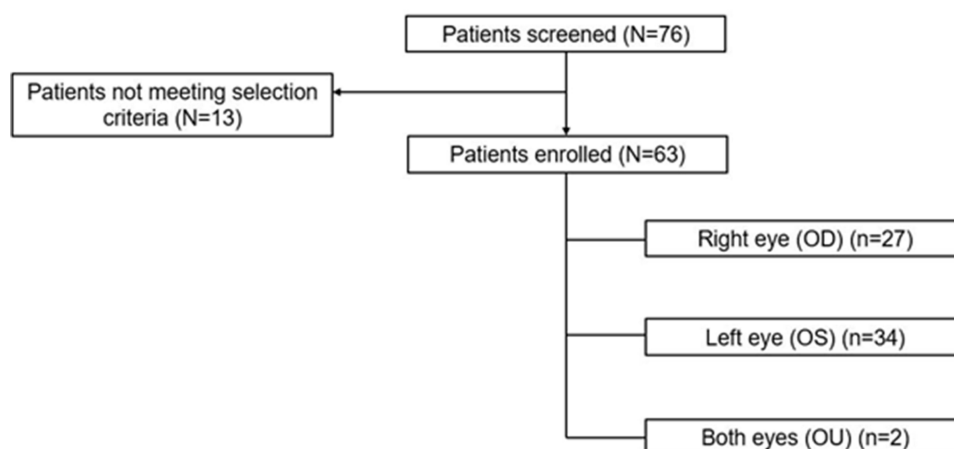


Figure 1 Study population.

eyes were treatment-naïve, and 40 (61.5%) eyes had received prior anti-VEGF therapy for nAMD. The mean age of patients was 69.16 ± 9.72 years. Ranibizumab was the most prescribed prior anti-VEGF (55.0% of eyes), followed by aflibercept (25.0% of eyes). No patients had a prior history of intraocular inflammation (IOI), retinal vascular occlusion, or retinal vasculitis (Table 1).

Changes in IRF, SRF, and PED at Month 3

Among all the 65 eyes, notable changes in IRF, SRF, and PED were observed as early as month 1 following the first brolocizumab injection. Around 27 (41.5%) and 36 (55.4%) eyes had decreased and complete IRF resolution, respectively, at the end of month 1. By the end of month 3, IRF decreased in 13 (20.0%) eyes and completely resolved in 50 (76.9%) eyes (naïve eyes: 76.0% and switch eyes: 77.5%). Similarly, at the end of month 1, SRF decreased in 39 (60.0%) eyes and resolved in 19 (29.2%) eyes. By the end of month 3, SRF decreased in 17 (26.1%) eyes and resolved in 42 (64.6%) eyes (naïve eyes: 64.0% and switch eyes: 65.0%). Further, PED decreased and resolved in 20 (30.7%) and 41 (63.1%) eyes, respectively, at the end of month 1 and decreased in 16 (24.6%) eyes and resolved in 44 (67.7%) eyes (naïve eyes: 60.0%

Table 1 Baseline Demographics and Disease Characteristics

Parameters	Total	OD	OS	OU
Patients [#]	63	27	34	2
Eyes [#]	65	27	34	4
Age (years)				
Mean \pm SD	69.16 \pm 9.72	69.07 \pm 8.91	69.24 \pm 10.56	69.00 \pm 2.00
Gender, n (%)				
Male	36 (57.14%)	13 (48.15%)	22 (64.71%)	1 (50.00%)
Female	27 (42.86%)	14 (51.85%)	12 (35.29%)	1 (50.00%)
Previous treatment				
Anti-VEGF naïve eyes	25 (38.5%)	14 (51.85%)	11 (32.35%)	0 (0%)
Prior treatment with anti-VEGF (switch eyes)	40 (61.53%)	13 (48.15%)	23 (67.75%)	4 (100%)
Total number of anti-VEGF injections received by the switch eyes	253	88	160	5

(Continued)

Table 1 (Continued).

Parameters	Total	OD	OS	OU
Prior anti-VEGF agent, n (%)				
Ranibizumab	22 (55.00%)	6 (46.15%)	14 (60.87%)	2 (50.00%)
Aflibercept	10 (25.00%)	5 (38.47%)	3 (13.04%)	2 (50.00%)
Bevacizumab	1 (2.50%)	–	1 (4.35%)	–
Biosimilar Ranibizumab	4 (10.00%)	1 (7.69%)	3 (13.04%)	–
Ranibizumab, Aflibercept	2 (5.00%)	1 (7.69%)	1 (4.35%)	–
Bevacizumab, Aflibercept, Ranibizumab	1 (2.50%)	–	1 (4.35%)	–
Visual complaints at first visit*	5 (7.69%)	4 (14.81%)	1 (2.94%)	0 (0%)
Comorbidities				
Hypertension	13 (20.00%)	7 (25.93%)	4 (11.76%)	2 (50.00%)
Diabetes Mellitus	9 (13.85%)	6 (22.22%)	1 (2.94%)	2 (50.00%)
Ischemic Heart Disease	5 (7.69%)	–	3 (8.82%)	2 (50.00%)
Psychological	3 (4.61%)	–	1 (2.94%)	2 (50.00%)
Hypercholesterolemia	3 (4.61%)	–	1 (2.94%)	2 (50.00%)
Hyperlipidaemia	3 (4.61%)	–	1 (2.94%)	2 (50.00%)

Notes: #Represents number. *None of the patients had prior intraocular inflammation, retinal vascular occlusion, or retinal vasculitis.

Abbreviations: Anti-VEGF, anti-vascular endothelial growth factor; SD, standard deviation; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque.

and switch eyes: 72.5%) at the end of month 3. The changes in IRF, SRF, and PED were statistically significant at month 3 compared to baseline ($p < 0.05$) (Figure 2). The percentage of eyes achieving dryness (absence of both IRF and SRF) increased from 9 (13.8%) at baseline to 34 (52.3%) eyes at the end of month 3 ($p < 0.001$). The details are provided in [Supplementary Table 1A–C](#). Amongst 65 eyes, only one PCV case was identified. Figures 3 and 4 are representative case examples of treatment-naïve and previously treated cases of nAMD who received brolocizumab, respectively.

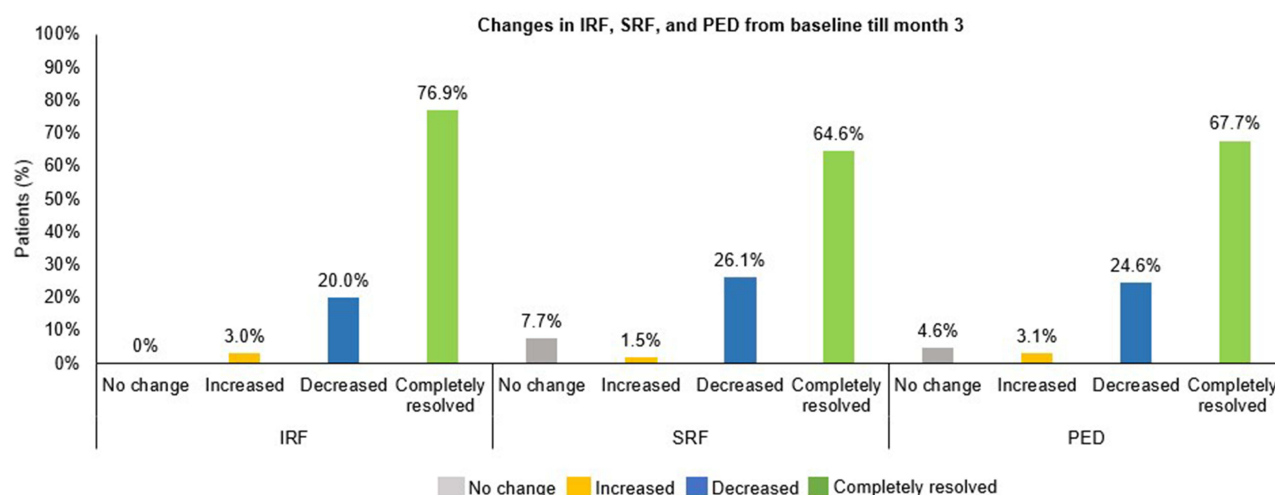


Figure 2 Changes in intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachment (PED) from baseline till month 3.

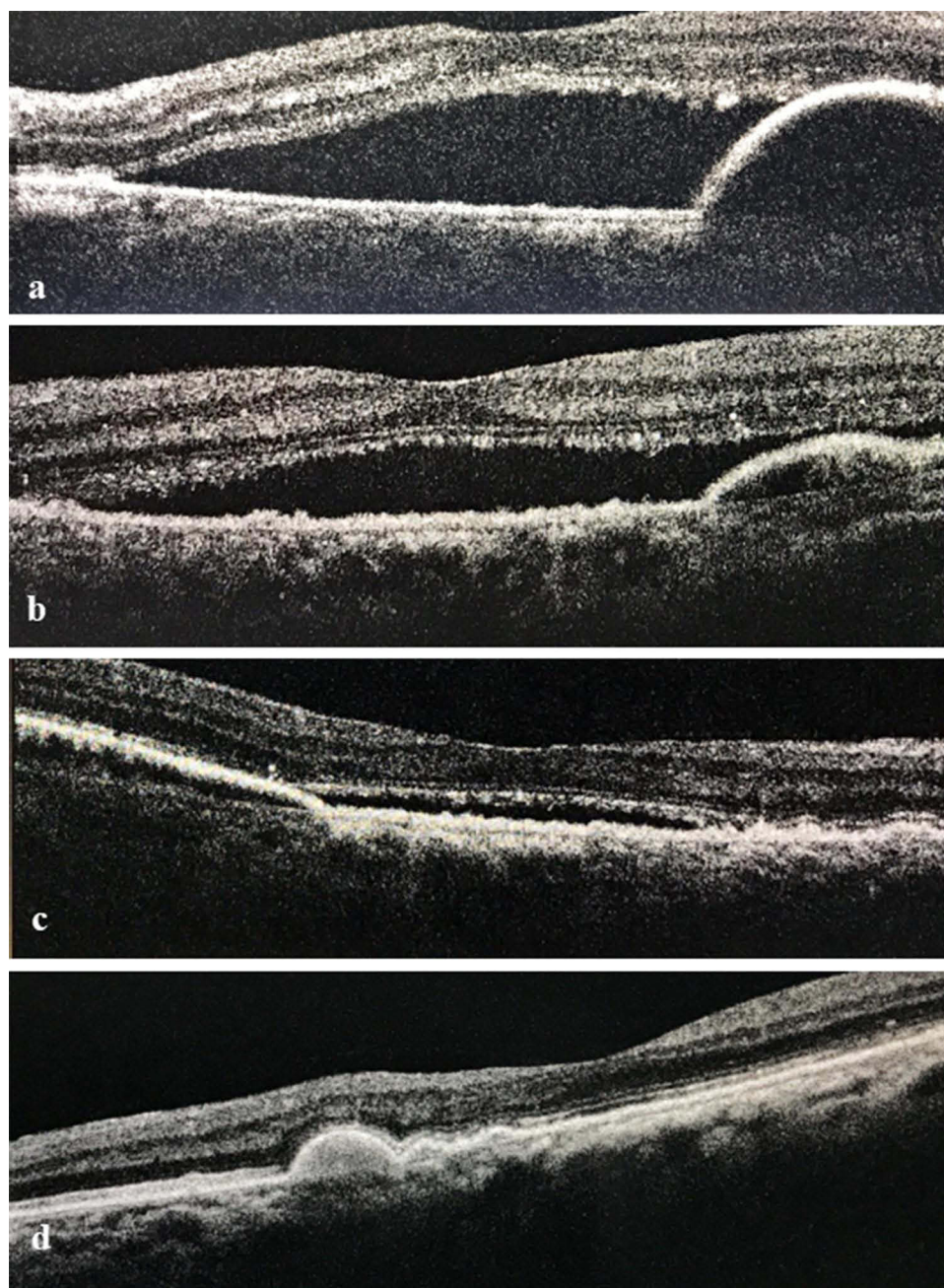


Figure 3 Representative case of a 72-year-old female, with a treatment-naïve PCV eye. (a) Baseline: spectral domain OCT (SD-OCT) image showing SRF, notch like PED; (b) follow-up 1: SD-OCT image at 4 weeks after Brolucizumab injection showing partial resolution of SRF along with significant reduction on PED height; (c) follow-up 2: SD-OCT image at 8 weeks after Brolucizumab injection showing minimal SRF and PED height further reduced; (d) follow-up 3: SD-OCT image at 12 weeks after Brolucizumab injection showing complete resolution of SRF and minimal RPE corrugation and flat macula.

Changes in BCVA and CRT from Baseline

A significant improvement in mean BCVA was observed at the end of month 3 compared to baseline (baseline: 0.7 ± 0.5 logMAR; month 3: 0.5 ± 0.4 logMAR, mean change: -0.2 ; $p < 0.001$) (Figure 5). Further, a significant reduction in mean CRT was also noted at the end of month 3 ($308.3 \pm 73.8 \mu\text{m}$) compared to baseline ($403.5 \pm 118.7 \mu\text{m}$) ($p < 0.001$) (Figure 6).

Number of Injections and Treatment Interval

At the end of month 3, a total of 82 injections were administered in 65 eyes. Overall, 52 (80.0%) eyes received a single injection, 9 (13.8%) eyes received two injections, and 4 (6.2%) eyes received three injections. The details are enlisted in Table 2. In the

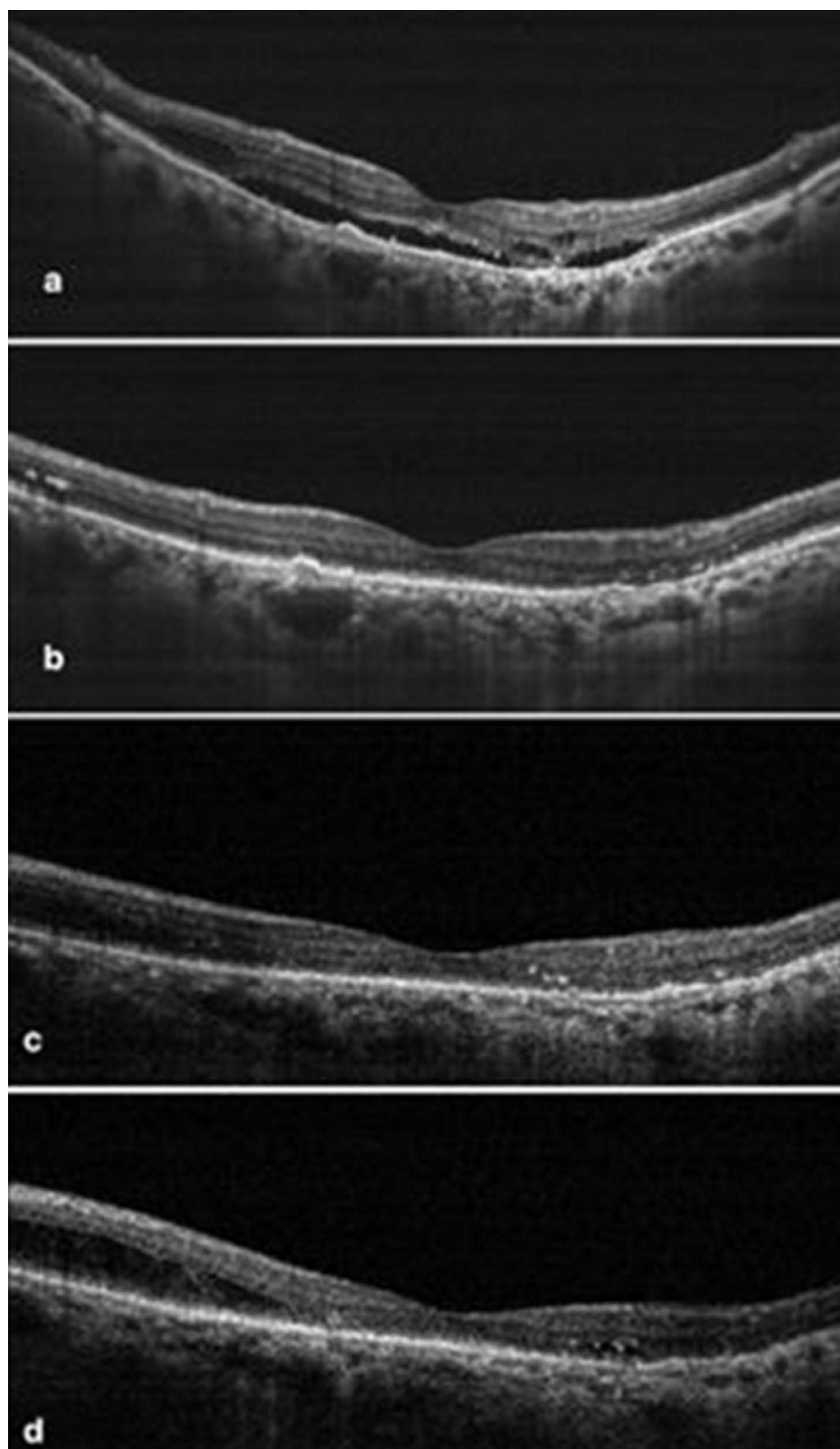


Figure 4 Representative case of nAMD who had previously received 5 anti-vascular endothelial growth factor (anti-VEGF) injections with suboptimal outcomes. After switching to brolucizumab, the study eye demonstrated complete resolution as compared to the baseline (a) Complete resolution of the subretinal and intraretinal fluid at week 4 (b) and week 8 (c). Early recurrence was noted at 12 weeks (d), for which the study eye received a second dose of brolucizumab. Also, the patient received 2 injections of brolucizumab during the 24-week follow-up.

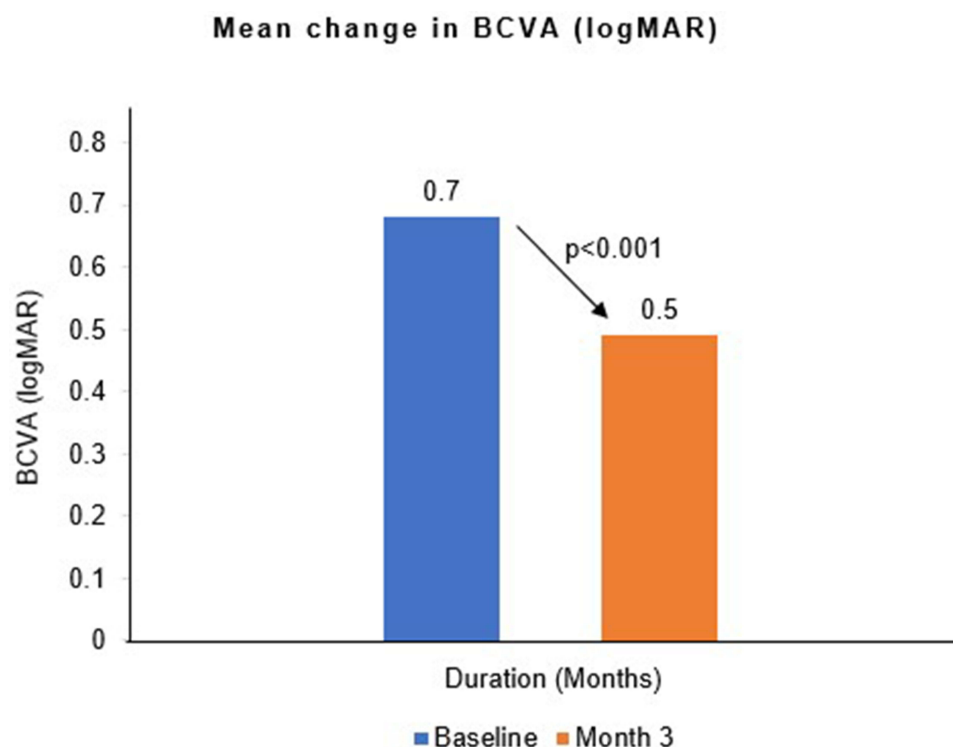


Figure 5 Mean best-corrected visual acuity (BCVA) from baseline till month 3.

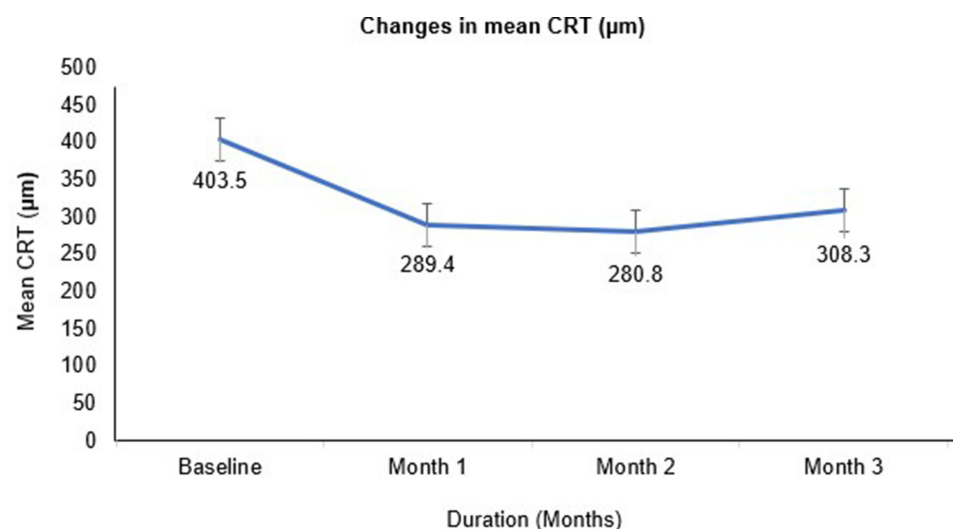


Figure 6 Mean change in central retinal thickness (CRT) as assessed by optical coherence tomography (OCT) from baseline till month 3 (N=65).

switch group (n = 40 eyes), prior to brolucizumab, a total of 253 anti-VEGF injections were administered (Table 1). The mean number of previous injections in the switch group was 6.66 (range: 1–15).

Monitoring Visits

In addition to the patient visits for brolucizumab injection, visits for monitoring or visits due to AEs were also captured during the first 3 months of treatment. Of the total 53 visits without anti-VEGF injections, 50 visits were for monitoring purposes by the end of month 3, and the remaining 3 visits were due to AEs during the 1st month.

Table 2 Brolucizumab Injection Details from Baseline to Month 3 (N = 65)

Parameters	Total	OD	OS	OU
Patients[#]	63	27	34	2
Eyes[#]	65	27	34	4
Baseline first brolucizumab injection: 0–30 days				
Yes	65 (100%)	27 (100%)	34 (100%)	4 (100%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Between 31 to 60 days (±15 days)				
Yes	6 (9.23%)	1 (3.70%)	5 (14.71%)	0 (0%)
No	59 (90.77%)	26 (96.30%)	29 (85.29%)	4 (100%)
Between 61 to 90 days (±15 days)				
Yes	11 (16.92%)	4 (14.81%)	5 (14.71%)	2 (50.00%)
No	54 (83.08%)	23 (85.19%)	29 (85.29%)	2 (50.00%)
Number of patients and injections and injection interval (weeks)				
Patients received only 1 injection[#]	51 (80.95)	23 (85.18%)	27 (79.41%)	1 (25.00%)
Eyes received only 1 injection[#]	52 (80.00%)	23 (85.18%)	27 (79.41%)	2 (50.00%)
Injections [#]	52	23	27	2
Patients received only 2 injections[#]	8 (12.70%)	3 (11.11%)	4 (11.76%)	1 (25.00%)
Eyes received only 2 injections[#]	9 (13.8%)	3 (11.11%)	4 (11.76%)	2 (50.00%)
Injections [#]	18	6	8	4
2 nd injection interval (weeks), Mean ± SD	8.54 ± 1.97	8.62 ± 0.33	7.57 ± 1.84	12.14
Patients received only 3 injections[#]	4 (6.35%)	1 (3.70%)	3 (8.82%)	0 (0%)
Yes received only 3 injections[#]	4 (6.15%)	1 (3.70%)	3 (8.82%)	0 (0%)
Injections [#]	12	3	9	0
2nd injection interval (weeks), Mean ± SD	6.43 ± 2.41	10.00	5.24 ± 0.44	–
3rd injection interval (weeks), Mean ± SD	4.79 ± 0.44	5.43	4.57 ± 0.14	–
Total injections[#]	82	32	44	6

Note: [#]Represents number.

Safety

Overall, 3 AEs were reported (retinal pigment epithelial rip, n = 1, and subretinal hemorrhage, n = 2). All the events occurred after the first injection of brolucizumab and were suspected to be related to the study drug. However, the drug was not discontinued in any of the cases. The patient with subretinal hemorrhage underwent a vitrectomy. Of note, no IOI was observed in any of the eyes.

Exploratory Analysis (Extended Follow-Up Up to Month 6)

The short-term effectiveness of brolucizumab injections on fluid levels, number of injections received, change in BCVA and CRT from baseline, and incidence of AEs were further evaluated for months 4, 5, and 6 in all 65 eyes (naïve eyes: 38.5% and switch eyes: 61.5%). During the month 4 to 6, 36 (55.4%) eyes received the second injection, and 2 (3.1%)

eyes received the third injection ([Supplementary Table 2](#)). None of the eyes had a reappearance of the fluids from months 4 to 6. Further, at the end of month 6, 38 (58.5%), 37 (56.9%), and 37 (56.9%) eyes sustained the resolution of IRF, SRF, and PED, respectively, as it was observed at month 3 [[Supplementary Table 3A–C](#)]. BCVA was observed to be reduced at the end of month 6 (0.5 logMAR) compared to baseline (0.7 logMAR) ($p < 0.001$). Further, a significant reduction in CRT was noted at the end of month 6 (288.51 μm) compared to baseline (403.5 μm) ($p < 0.001$) ([Supplementary Table 4](#)). No additional adverse events were reported between month 3 to month 6.

Discussion

The present real-world study provides insights on the short-term effectiveness of brolucizumab for the treatment of nAMD in 82 patient eyes from 4 centres in India and reports statistically significant improvement in anatomical and visual outcomes at the end of month 3 compared to baseline. Additionally, the study found that 3/82 eyes experienced AEs, which did not require discontinuation of brolucizumab. Both treatment-naïve and switch eyes responded positively to the brolucizumab treatment. At the end of month 3, $\geq 65\%$ of eyes had shown complete resolution of IRF, SRF, and PED with brolucizumab therapy, including switch eyes. These observed improvements in fluid levels were found to be sustained up to month 6. Of the total 65 eyes, 80.0% ($n = 52$) required only one injection and did not require a second injection during the 3 months of study duration.

This retrospective real-world study in Indian nAMD patients measured the short-term effectiveness of brolucizumab with fluid status as the primary endpoint over a period of three months. Though the study population differed from other real-world studies such as BRAILLE,¹⁵ PROBE³³ and REBA³⁴ [current study; naïve eyes 38.5% and switch eyes 61.5%; BRAILLE: naïve eyes: 21.3% and switch eyes: 78.7% and REBA: naïve eyes: 23.8% and switch eyes: 76.2%, PROBE: 27 eyes] the outcomes were comparable to that of BRAILLE, REBA, and PROBE.^{15,33,34}

IRF

In our study, IRF was resolved in half of the total 65 eyes at the end of month 1 [36 (55.4%) eyes] and was completely resolved in three-fourth of the eyes [50 (76.9%) eyes] at the end of month 3, which was a statistically significant compared to the baseline ($p < 0.05$). When compared with the BRAILLE study, complete IRF resolution was observed in 39.3% of eyes at the final follow-up visit.¹⁵ Similarly, in a study conducted by Montes et al, IRF was present in 12 out of 19 (63.2%) eyes at baseline and got resolved in 9 (47.4%) eyes at the last follow-up.³⁰

SRF

In the current study, of the 65 eyes with SRF at baseline, brolucizumab led to a reduction in 17 (26.1%) eyes and complete resolution in 42 (64.6%) eyes, whereas there was minimal/no change in 5 (7.7%) eyes at the end month 3. The BRAILLE study reported similar outcomes with reduction observed in 78.9% of eyes, complete SRF resolution in 15.5% of eyes, and no/minimal change in 5.6% of eyes.¹⁵

PED

In the present study, PED was observed to decrease in 16 (24.6%) eyes and resolved in 44 (67.7%) eyes at the end of month 3, which was significantly different compared to baseline ($p < 0.05$). Similarly, in the BRAILLE study, PED was reported to be reduced in 61.9% of eyes and resolved in 23.8% of eyes.¹⁵

BCVA

A significant improvement in BCVA from baseline to month 3 was noted in the present study (baseline: 0.7 ± 0.5 logMAR; month 3: 0.5 ± 0.4 logMAR; $p < 0.001$) which was similar to that observed in the BRAILLE study (baseline: 0.8 ± 0.5 logMAR; final: 0.7 ± 0.51 logMAR; $p < 0.00001$). Likewise, in another retrospective, real-life clinical study, the mean BCVA was reported to be significantly improved from 0.24 ± 0.27 logMAR at baseline to 0.12 ± 0.23 logMAR at month 3 post-brolucizumab injection ($p < 0.001$).²⁹ In a retrospective, multicentric PROBE study, a significant gain in the mean BCVA was seen in treatment naïve patients undergoing brolucizumab therapy ($p = 0.014$).³³ Additionally, in REBA study, there was a significant gain in mean BCVA in the treatment naïve and switch therapy groups following brolucizumab

treatment.³⁴ However, there was no evidence of visual benefits after brolucizumab administration in RWE studies conducted by Walter et al,³⁵ Bulirsch et al,²⁷ Enriquez et al,²⁸ and Sharma et al.²⁶

CRT

A significant reduction was noted in CRT at month 3 ($308.3 \pm 73.8 \mu\text{m}$) compared to baseline ($403.5 \pm 118.7 \mu\text{m}$) ($p < 0.001$) in the present study. Similar observations were reported in another real-world clinical study, wherein CRT decreased significantly from $461.7 \pm 82.9 \mu\text{m}$ to $343.6 \pm 74.3 \mu\text{m}$ ($p = 0.004$) 3 months after the treatment.³⁶

Further, the extended analysis carried out in the present study demonstrated that none of the study eyes had reappearance of the fluids till month 6. Moreover, the improvements in outcomes such as BCVA and CRT observed at the end of month 3 were maintained till month 6. These findings were in concurrence with the observations of a study carried out by Abdin et al, wherein, all outcomes mentioned above were found to improve till 1 year post the first administration of brolucizumab among patients with nAMD.³⁷ The current study findings were also consistent with the BRAILLE study conducted in Indian patients over 52 weeks wherein brolucizumab demonstrated significant improvement in BCVA with significant reductions in CST, SRF, and IRF.³⁸

Safety Outcomes

Brolucizumab was observed to have a favorable benefit-risk profile, with 3 AEs (retinal pigment epithelial rip, $n = 1$, and subretinal hemorrhage, $n = 2$) reported during the entire course of treatment. Study results were within the known safety profile, and no new safety signal was identified. Similar AEs were reported in HAWK and HARRIER clinical trials following brolucizumab therapy.²¹ A short-term study conducted by Montesel et al had reported an intra-ocular inflammation following intravitreal brolucizumab.³⁰ In a recent real-world study of brolucizumab safety in the 12–18 months after treatment initiation in the US reported a proportion of IOI-related AEs in 22 (4.6%) eyes out of 482 eyes. Majority of the eyes [14/22 (64%)] developed IOI-related AE within 90 days of the first brolucizumab injection of which 3 (14%) AE developed in the first 30 days.²⁴ Additionally, REBA study noted two adverse events,³⁴ whereas in another retrospective study by Sharma et al no AE was reported.²⁶ Bauman et al in a systematic review documented the incidence of IOI ranging from 0% to 19%.²³

The difference in the incidence of adverse events between this study and other studies may be attributed to variations in patient characteristics, limited sample size, as well as lower number of injections with monthly follow-ups. Additionally, since brolucizumab was approved in India in July 2020, it is likely that following the reporting of the safety signal for brolucizumab in February 2020, Indian clinicians may have benefitted with information on potential risks and better understanding of IOI and related adverse events. Evidence-based recommendations developed by various groups of ophthalmologists, providing guidance on patient selection, thorough examination of the eye for inflammation prior to injection and patient education on self-monitoring of symptoms, and report symptoms as soon as they develop, might have contributed to lower incidence of events in the real-world settings.

This current study also demonstrated that the real-world usage pattern of brolucizumab in Indian nAMD patients departs from the per-label usage.³⁹ If the injections were given as per label, which recommends a loading phase of 3 injections 4 weeks apart, we would have observed about 3–4 injections per eye instead of 1 for most patient eyes. The finding that effectiveness outcomes at 3 months have still showed improvement (despite the less frequent injections and ~62% switch eyes) compared to outcomes before the start of brolucizumab is noteworthy and can be helpful for clinicians and their patients in weighing the benefits and risks of starting this therapy given it is also associated with a risk of adverse event. Given the patient's socioeconomic status, chronic nature of the disease, burden of frequent injections, and visits imposed on patients and caregivers, as well as poor treatment compliance, and out-of-pocket expenditure, exploring the early effectiveness and safety outcomes of brolucizumab in real world Indian settings is pivotal.^{16,40}

Strengths and Limitations

The strengths of the study include having a heterogeneous sample of patient eyes from 4 centres and capturing the short-term outcomes from real-world practice in India, where injection and follow-up visits are at the discretion of the treating clinician. The major limitations of the present study are its retrospective nature, limited sample size, and brief follow-up period. Other limitations include OCT evaluation done at individual centre by a single grader from each centre.

Conclusions

This real-world short-term study reported significant improvements in fluid parameters from baseline to month 3 in both treatment-naïve eyes and eyes who had received prior anti-VEGF injections. Further, a marked improvement was also observed in BCVA along with a significant reduction in CRT at the end of month 3 compared to the baseline. Brolucizumab was observed to have a favorable benefit-risk profile, and the study results were in line with the known safety profile of the drug, with no IOI reported during the study duration. Notably, the study emphasized the significance of brolucizumab in addressing the unmet need for nAMD treatment as it has the potential to reduce the treatment burden of frequent injections and improve patient compliance. However, further prospective studies with larger sample size and with long-term follow-up and comparative arms may provide better assessment and sustainability of the effectiveness outcomes and benefits in real-world practice.

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Disclosure

Maulik Bhavsar is an employee of Novartis Healthcare Pvt Ltd. India. Helene Karcher is an employee and shareholder of Novartis Pharma AG, Switzerland and Editor-in-Chief of the journal *Epidemiologic Methods*, a scientific journal from the publishing company De Gruyter. Helene Karcher receive a yearly honorary for this service. The other authors report no conflicts of interest in this work.

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