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ORIGINAL RESEARCH

Real-World Safety Outcomes with Brolucizumab in Neovascular Age-Related Macular Degeneration: Findings from the IRIS® Registry

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ABSTRACT

Introduction: To assess real-world safety outcomes for adults with neovascular age-related macular degeneration (nAMD) treated with brolucizumab from the US-based IRIS® (Intelligent Research in Sight) Registry.

Methods: In this retrospective study, 18,312 eyes (15,998 patients) treated with ≥ 1 intravitreal brolucizumab injections between 8 October 2019 (US launch date for brolucizumab) and 7 October 2021 were followed up for ≤ 2 years after first injection (index date). The study assessed the predefined incident ocular adverse events of intraocular inflammation (IOI), retinal vasculitis (RV), and retinal vascular occlusion (RO).

Results: Overall, 614/18,312 eyes (3.4%) experienced any IOI, RV, and/or RO event. Median (interquartile range [IQR]) time to an event was

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84 (42–167) days; 77.4% of events (475/614) occurred within 6 months after index date. Median (IQR) number of brolucizumab injections before an event was 2 (1–4). For eyes with an adverse event and visual acuity (VA) data (n = 406), median (IQR) change in Early Treatment of Diabetic Retinopathy Study (ETDRS) letters from pre-event VA was 0 (− 7 to + 5) at the 6-month follow-up; 50 eyes (12.3%) had a VA loss of 10 or more ETDRS letters. Risk of an event (hazard ratio [95% confidence interval]) was decreased in eyes from male patients (0.61 [0.53–0.71]), from older patients (0.83 [0.76–0.90]), from treatment-naive patients (0.51 [0.38–0.69]), and from patients who started brolucizumab in the second year after launch (0.68 [0.53–0.86] vs. first year).
Conclusion: In this large real-world brolucizumab safety study, 3.4% of eyes experienced an IOI, RV, and/or RO event. Among eyes that experienced an adverse event for which VA data were available, median ETDRS vision change was 0 letters (IQR − 7 to + 5).

Keywords: Anti-vascular endothelial growth factor therapy; Brolucizumab; Intraocular inflammation; Neovascular age-related macular degeneration; Real-world evidence

Key Summary Points

Why carry out this study?

Retinal vasculitis (RV) and/or retinal vascular occlusion (RO) adverse events have been observed following brolucizumab treatment for neovascular age-related macular degeneration (nAMD) that could lead to loss of vision.

This study aimed to gain a better understanding of the occurrence of these events and their effects on vision during long-term brolucizumab treatment in real-world clinical practice using US registry data.

What was learnt from the study?

In this study in over 18,000 eyes with nAMD, 3.4% of eyes experienced an intraocular inflammation (IOI), RV, and/or RO event during up to 2 years of follow-up, with the majority of events occurring within 6 months after treatment initiation.

Among eyes with an IOI, RV, and/or RO event and data available on visual acuity, the median change in Early Treatment of Diabetic Retinopathy Study (ETDRS) vision score was 0 letters.

Risk of an IOI, RV, and/or RO event was decreased in eyes from male patients, in treatment-naive eyes, and in eyes from older patients; the risk of an event was also lower for patients who started brolucizumab in the second year after US launch compared with the first year.

INTRODUCTION

Brolucizumab, an anti-vascular endothelial growth factor (VEGF) therapy, was approved for the treatment of neovascular (wet) age-related macular degeneration (nAMD) based on data from the pivotal phase 3 HAWK and HARRIER clinical trials [1, 2]. Following its launch in the USA in October 2019, Novartis (Basel, Switzerland) received post-marketing reports from routine clinical practice of retinal vasculitis (RV), including retinal occlusive vasculitis, following intravitreal treatment with this molecule [3, 4]. A review of post-marketing safety case reports conducted by Novartis in partnership with an external safety review committee (SRC) concluded that there was a confirmed safety signal of RV and/or retinal vascular occlusion (RO) adverse events with brolucizumab, typically in the presence of intraocular inflammation (IOI), that could result in severe vision loss [3]. A post hoc review of the HAWK and HARRIER studies by the SRC reported an

overall incidence of 4.6% for IOI, 3.3% for IOI with RV, and 2.1% for IOI with RV and RO [5].

A retrospective analysis of safety outcomes with brolucizumab in real-world clinical practice in the USA using two large healthcare databases (the Intelligent Research in Sight [IRIS®] Registry and the Komodo Healthcare Map) reported an overall incidence of 0.6% for RV and/or RO events, and 2.4% for any form of IOI (including RV) and/or RO [6]. However, this prior analysis covered patients who had initiated brolucizumab treatment during the first 8 months after its US launch, and the median follow-up time was only 3 months (maximum: 6 months). Thus, the report represents early real-world experience with brolucizumab soon after its launch, with much of the study duration covering the period before awareness of the safety signal with brolucizumab [6].

The aim of the current study was to expand on the previous IRIS Registry analysis and assess real-world safety outcomes with brolucizumab over a longer treatment period while investigating potential risk factors in a larger sample size. The primary objective was to evaluate incident, predefined ocular safety events, together with vision outcomes following these events, in all patient eyes in the IRIS Registry database receiving at least one brolucizumab injection for nAMD in the first 2 years after its US launch. In addition, this study aims to assess the impact of age, sex, prior anti-VEGF therapy and time of first brolucizumab injection (first vs. second year after launch) on the likelihood for an eye to experience an event.

METHODS

IRIS Registry

This study analyzed data from the American Academy of Ophthalmology IRIS Registry, which is a centralized, national US registry specifically for eye diseases and conditions [7, 8]. The registry contains de-identified eye-level patient data from electronic health records collected from participating ophthalmology practices across the USA [9]. Data are collected in accordance with the Health Insurance Portability and Accountability Act (HIPAA) [10]. Approximately 70% of the 18,000 practicing ophthalmologists in the USA contribute to the IRIS Registry [9], and it is thought to include 70–80% of patients with nAMD in the USA.

This study complied with the tenets of the Declaration of Helsinki. The analysis was based on de-identified patient data, and this study was reviewed and deemed exempt by the Western-Copernicus Group (WCG) Institutional Review Board (Puyallup, WA, USA) [11]. Informed consent was not required as the analysis was based on de-identified patient data.

Study Population

Patient eyes that had received at least one intravitreal injection of brolucizumab between 8 October 2019 (the US launch date for brolucizumab) and 7 October 2021 were identified from the IRIS Registry. For inclusion in the analysis, the patient (eyes) had to be at least 18 years old at the date of the first brolucizumab injection (index date); have received a diagnosis of nAMD in the 36 months before or on the index date; and have known disease laterality at the index injection. Patient eyes that had been treated with brolucizumab before 8 October 2019 (e.g., in clinical trials) were excluded. All eligible patient eyes were included in the analysis irrespective of whether the patient had received unilateral or bilateral treatment in order that the risks of brolucizumab in all actual real-world cases would be reported and analyzed.

For additional analysis, eligible patient eyes were also divided into two sub-cohorts according to whether their index brolucizumab injection was during the first or second year after the US launch of brolucizumab (Year 1 sub-cohort: 8 October 2019 to 7 October 2020; Year 2 sub-cohort: 8 October 2020 to 7 October 2021). Patients were followed up until the end of the study period or their last documented encounter in the registry. The cut-off date for last follow-up in the study analysis was 30 September 2022. The end date of 7 October 2021 for brolucizumab initiation was chosen to ensure that all eyes had the possibility of at least

12 months of follow-up at the time of the analysis.

Definitions of Ocular Adverse Events

This safety analysis evaluated the following predefined incident ocular adverse events: IOI, endophthalmitis, RV, and RO (referred to collectively throughout the text as IOI, RV, and/or RO events for conciseness). Events were identified using diagnostic codes from the International Statistical Classification of Diseases, Tenth Revision (ICD-10) (see Electronic Supplementary Material [ESM] Table S1 for details) and were the same as those used in the earlier registry analysis of safety outcomes with brolucizumab [6]. Events were considered to be incident events if there were no reports of the event in the 12 months before the index date. This definition was used to avoid the carry-over of pre-existing conditions or complications and to help ensure that the events analyzed were true new events.

Outcome Measures

Outcome measures included the number (%) of patient eyes with any adverse event of interest, time to an event from the index date, the number of prior brolucizumab injections for eyes with an event, and changes in visual acuity (VA) for eyes at or immediately following an event and 6 months after an event.

VA change following the event was calculated as the difference between the 'event VA' (defined as the best-recorded VA [BRVA] reading closest to the event date, within 0–45 days after the event date) and the 'pre-event VA' (the BRVA reading closest to and before the event date, taken on or after the index date). Long-term change in VA after the event was the difference between the 'post-event VA' (the BRVA reading closest to 6 months after the event date [± 45 days]) and the 'pre-event VA'.

Outcome measures were analyzed for the full study cohort and the two sub-cohorts and are presented here at the patient eye level. The relative risk for an eye to experience an event over time was analyzed for the full cohort, with the population stratified according to age, sex, prior anti-VEGF therapy (previously treated vs. treatment-naive), or time of index injection (first vs. second year after launch).

Statistical Analysis

Baseline demographic and clinical characteristics and outcome variables were tabulated using descriptive statistics. No data imputation was performed for missing values. Adverse event outcome measures were analyzed over a maximum follow-up period of 2 years for the full cohort; for the sub-cohorts, this period was 1 year to control for differences in the maximum possible follow-up duration between the two sub-cohorts. A Cox proportional hazards model was used to assess the hazard ratio (HR) for an eye to experience an event over time. The model included as covariates age group at index date (in decade increments starting at 18 years of age), sex, prior anti-VEGF therapy (previously treated vs. treatment-naive), and time of index injection (first vs. second year after launch). Eyes belonging to the same patient were assigned to clusters in the model to account for the intercorrelation of their outcomes. *P* values are reported as nominal *P* values. Data were analyzed by Verana Health using Python 3.7 (Python Software Foundation; Fredericksburg, VA, USA) and Apache Spark 2.4.5 (Apache Software Foundation; Forest Hill, MD, USA).

RESULTS

Baseline Characteristics

A total of 18,312 eyes in 15,998 patients were included in the full study cohort (Table 1). Most eyes (89.0%) received their first brolucizumab injection during the first year after the US launch of this molecule, and some differences in baseline VA and prior treatment were observed between the Year 1 and Year 2 sub-cohorts (Table 1). Compared with the Year 1 sub-cohort, the Year 2 sub-cohort had a higher proportion of treatment-naive eyes, a slightly lower index VA score, and a higher proportion

Table 1 Baseline demographics and characteristics

Variables	Full cohort	Year 1 sub-cohort	Year 2 sub-cohort
Number of patient eyes	18,312	16,291	2021
Age at index date[a,b]			
Mean ± SD, years	79.7 ± 7.6	79.8 ± 7.5	78.6 ± 8.5
< 65 years *n* (%)	658 (3.6%)	540 (3.3%)	118 (5.8%)
65–74 years, *n* (%)	3734 (20.4%)	3282 (20.1%)	452 (22.4%)
75–84 years, *n* (%)	7673 (41.9%)	6801 (41.7%)	872 (43.1%)
≥ 85 years, *n* (%)	6247 (34.1%)	5668 (34.8%)	579 (28.6%)
Sex[b]			
Female	10 455 (57.1%)	9365 (57.5%)	1090 (53.9%)
Male	7857 (42.9%)	6926 (42.5%)	931 (46.1%)
Index visual acuity (ETDRS letter score)[c]			
Eyes with available data, *n* (%)	12 801 (69.9%)	11 516 (70.7%)	1285 (63.6%)
Median (IQR) ETDRS letters	65 (55–76)	65 (55–76)	61 (45–70)
ETDRS letter score, *n* (%)			
95 or better	3 (< 0.1%)	3 (< 0.1%)	0 (0.0%)
85–95	605 (4.7%)	552 (4.8%)	53 (4.1%)
70–80	4996 (39.0%)	4594 (39.9%)	402 (31.3%)
40–65	5394 (42.1%)	4827 (41.9%)	567 (44.1%)
35 or worse	1803 (14.1%)	1540 (13.4%)	263 (20.5%)
Missing	5511 (30.1%)	4775 (29.3%)	736 (36.4%)
Time since nAMD diagnosis[d]			
Median (IQR), days	921 (401–1071)	948 (440–1071)	613 (161–1054)
< 6 months, *n* (%)	2492 (13.6%)	1960 (12.0%)	532 (26.3%)
6 to < 12 months, *n* (%)	1760 (9.6%)	1516 (9.3%)	244 (12.1%)
12 to < 24 months, *n* (%)	3180 (17.4%)	2848 (17.5%)	332 (16.4%)
≥ 24 months, *n* (%)	10 880 (59.4%)	9967 (61.2%)	913 (45.2%)
Prior treatment status			
Prior anti-VEGF treatment, *n* (%)	16 738 (91.4%)	15 139 (92.9%)	1599 (79.1%)
Treatment-naive, *n* (%)	1574 (8.6%)	1152 (7.1%)	422 (20.9%)
Time since first anti-VEGF injection[e]			
Median (IQR), days	793 (335–793)	825 (373–825)	486 (87–486)
< 6 months, *n* (%)	2968 (16.2%)	2332 (14.3%)	636 (31.5%)
6 to < 12 months, *n* (%)	1917 (10.5%)	1679 (10.3%)	238 (11.8%)

Table 1 continued

Variables	Full cohort	Year 1 sub-cohort	Year 2 sub-cohort
12 to < 24 months, *n* (%)	3613 (19.7%)	3298 (20.2%)	315 (15.6%)
≥ 24 months, *n* (%)	9814 (53.6%)	8982 (55.1%)	832 (41.2%)
Time on brolucizumab[f]			
Median (IQR), days	156 (70–361)	147 (69–336)	250 (119–399)

ETDRS Early Treatment of Diabetic Retinopathy Study, *IQR* interquartile range, *nAMD* neovascular age-related macular degeneration, *SD* standard deviation, *VA* visual acuity, *VEGF* vascular endothelial growth factor

[a]Index date is the date of the first brolucizumab injection

[b]Unit of analysis was patient eyes

[c]VA reading taken up to 30 days before or on the index date

[d]Time between first nAMD diagnosis in the 3-year baseline period and index date

[e]Time between first anti-VEGF injection and index date

[f]Time from index date to date of switch or 6 months after last date of brolucizumab injection or last date of follow-up

of eyes with an Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score of 35 or worse (Table 1).

Ocular Adverse Events

In the full cohort, 614 out of 18,312 patient eyes (3.4%) experienced any IOI, RV, and/or RO event during up to 2 years of follow-up after the first brolucizumab injection (Table 2). Among the 2314 patients who had received bilateral brolucizumab treatment, 142 eyes (out of 4628; 3.1%) experienced an IOI, RV, and/or RO event.

Overall, median time to an event was 84 (IQR 42–167) days (Table 2), with 53.7% and 77.4% of events (330/614 and 475/614) occurring within the first 3 and 6 months, respectively, after the index date (Fig. 1; ESM Table S2). The median number of brolucizumab injections before an event was 2 (IQR 1–4), with 58.5% of events (359/614) occurring after either one or two injections (Table 2; ESM Table S3).

Of the 614 eyes with an event, 100 eyes experienced an RV and/or RO event (overall incidence: 0.5%, 100/18,312) (Table 2). Median time to an RV and/or RO event was 99 (IQR 56–181) days (Table 2), with 43.0% and 75.0% of events (43/100 and 75/100) occurring within 3 and 6 months, respectively, of the first brolucizumab injection (ESM Fig. S1; ESM Table S2). Eyes received a median of two (IQR 2–3) brolucizumab injections before an RV and/or RO event, with 56.0% of events (56/100) occurring after either one or two injections (Table 2; ESM Table S3).

In the sub-cohort analysis, patient eyes were followed up for up to 1 year after the index date. The incidence of any IOI, RV, and/or RO event was 3.1% (506/16,291 eyes) in the Year 1 sub-cohort and 2.6% (53/2021) in the Year 2 sub-cohort; the incidence of an RV and/or RO event was 0.5% (85/16,291) and 0.4% (8/2021), respectively (Table 2). Median time to an IOI, RV, and/or RO event was shorter in the Year 2 sub-cohort (62 days; IQR 35–108) compared with the Year 1 sub-cohort (76 days; IQR 40–140), although the majority of events (> 84%) in both sub-cohorts occurred within 6 months after starting brolucizumab (Table 2; ESM Table S4). Similar findings were observed for RV and/or RO events (Table 2; ESM Tables S3, S4).

VA Changes in Patient Eyes Following an Event

Data for the long-term change in VA after an IOI, RV, and/or RO event were available for 406 of 614 (66.1%) eyes in the full cohort. The median change in ETDRS letter score from pre-

Table 2 Ocular adverse events (number of eyes with an event, time to event, and number of prior brolucizumab injections) during the follow-up after brolucizumab injection

Variables	Full cohort[a]	Year 1 sub-cohort[b]	Year 2 sub-cohort[b]
Number of patient eyes	18,312	16,291	2021
Eyes without an event, *n* (%)	17,698 (96.6%)	15,785 (96.9%)	1968 (97.4%)
Eyes with an event, n (%)			
IOI or endophthalmitis or RV or RO	614 (3.4%)	506 (3.1%)	53 (2.6%)
- RV and/or RO	100 (0.5%)	85 (0.5%)	8 (0.4%)
Median (IQR) time to an event, days[c]			
IOI or endophthalmitis or RV or RO	84 (42–167)	76 (40–140)	62 (35–108)
- RV and/or RO	99 (56–181)	98 (56–167)	70 (35–99)
Median (IQR) number of brolucizumab injections before an event			
IOI or endophthalmitis or RV or RO	2 (1–4)	2 (1–3)	2 (1–3)
- RV and/or RO	2 (2–3)	2 (1–3)	3 (1–3)

IOI Intraocular inflammation, *IQR* interquartile range, *RO* retinal vascular occlusion, *RV* retinal vasculitis
[a]Up to 2 years of follow-up
[b]Up to 1 year of follow-up
[c]From first brolucizumab injection

event VA was 0 (IQR − 7 to + 5), and 12.3% of eyes ($n = 50$) showed a VA loss of at least 10 ETDRS letters from their pre-event score at long-term (6-month) follow-up. In the full cohort, VA changes following the event were similar to those seen on long-term follow-up; analyses also showed similar VA changes at both assessments across the two sub-cohorts (ESM Table S5).

Relative Risk of an Event

The risk of experiencing an IOI, RV, and/or RO event was lower in men than in women (HR [95% CI] 0.61 [0.53–0.71]; $p < 0.005$) (Fig. 2). Treatment-naive eyes had a lower risk of an event than eyes previously treated with anti-VEGF therapy (0.51 [0.38–0.69]; $p < 0.005$), and the risk of events was lower for eyes treated in the second year compared with the first year after launch of brolucizumab (0.68 [0.53–0.86]; $p < 0.005$). The risk of events decreased with increasing age, with each 10-year increment starting from 18 years of age associated with a reduction in risk (0.83 [0.76–0.90]; $p < 0.005$). Time-to-event graphs, stratified according to sex, prior anti-VEGF therapy, and timing of the index date, are shown in ESM Fig. S2.

DISCUSSION

This registry study reports real-world safety outcomes from over 18,000 patient eyes with nAMD that were treated with brolucizumab in clinical practice in the USA over a 2-year period. This data set represents the largest population of eyes treated with brolucizumab in real-world practice studied to date. By using data from the national IRIS Registry (which covers an estimated 70% of ophthalmologists in the USA [9]), the study population is representative of the broader US population of patients with nAMD treated with brolucizumab.

The incidence of IOI, RV, and RO events in the current study was slightly lower than reported in the post hoc safety review of the HAWK and HARRIER clinical trials in treatment-naive patients with nAMD, although the

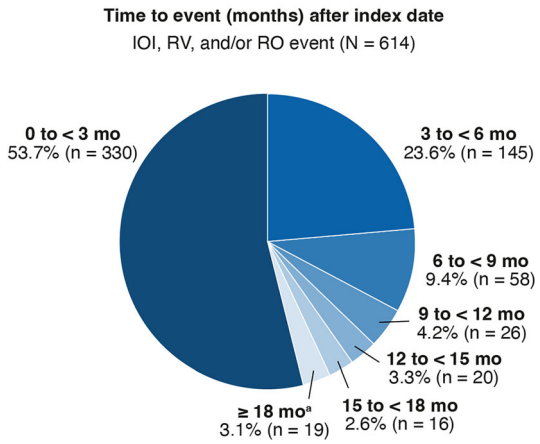

Fig. 1 Time to an IOI, RV, and/or RO event after the first brolucizumab injection. Chart shows the number and proportion (%) of eyes with an IOI, RV, and/or RO event in each time period after index date (out of a total of 614 eyes with an event). [a]Maximum time to an event was 728 days (23.9 months) after brolucizumab initiation. *IOI* Intraocular inflammation, *mo* months, *RO* retinal vascular occlusion, *RV* retinal vasculitis

timing of events after the initial brolucizumab injection was similar in both analyses [5]. A previous analysis of the IRIS Registry and Komodo databases, involving over 10,000 patient eyes, reported a lower incidence for any IOI event (2.4%) and a shorter median time to event (39 days) than the current analysis [6]. However, the earlier analysis was conducted soon after the US launch of brolucizumab, and the maximum follow-up period was only 6 months, with a median follow-up of 3 months.

A systematic review of real-world studies of brolucizumab treatment reported a wide variation in the incidence of IOI events (0–19%) [12]. However, the majority of these studies were small, had variable follow-up times, and were conducted across countries with differing clinical practices which may have impacted overall event rates. By comparison, larger, more recent real-world studies have shown findings similar to those of the current analysis. A retrospective analysis of 482 eyes from a large US retinal practice reported that 21 eyes (4.6%) had IOI-related adverse events, of which four eyes (0.8%) had concomitant RV and/or RO, during up to 18 months of follow-up [13]. A multicenter, retrospective analysis of 1098 eyes conducted in the Czech Republic reported an overall incidence of 3.83% for any IOI and 0.82% for IOI with RV, over a mean follow-up of 4 months [14].

In the current study, the median change in ETDRS letter score after an IOI, RV, and/or RO event was 0 from pre-event VA, although 12.3% of eyes with an adverse event lost at least 10 ETDRS letters from their pre-event score at long-term follow-up. This result indicates that although the occurrence of such an event can have a detrimental effect on vision, the majority of eyes with available data (87.7%) did not lose 10 or more ETDRS letters. Expert guidance on the use of brolucizumab, developed in response

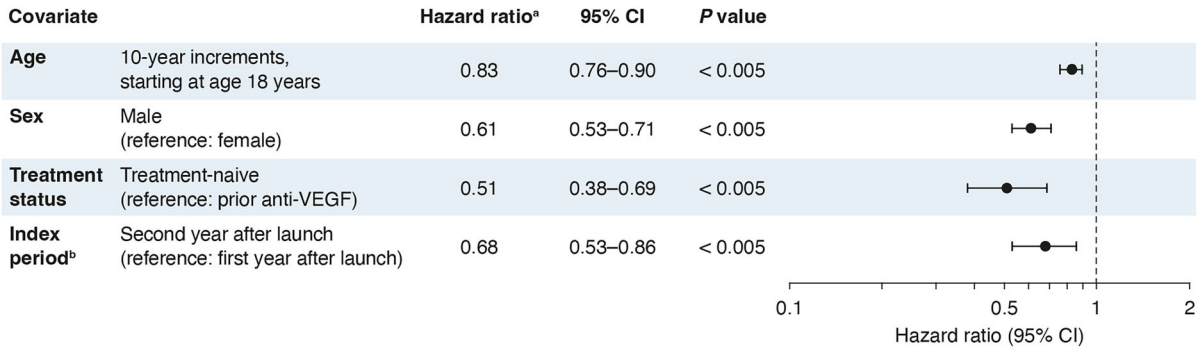

Fig. 2 Relative risk of an IOI, RV, and/or RO event (Cox proportional hazards model). [a]Hazard ratio < 1 indicates a reduced risk of an IOI, RV, and/or RO event. [b]Timing of the date of the first brolucizumab injection (index date). *CI* Confidence interval, *IOI* intraocular inflammation, *RO* retinal vascular occlusion, *RV* retinal vasculitis, *VEGF* vascular endothelial growth factor

to reports of IOI-related events, highlights the importance of prompt and aggressive treatment of IOI, RV, and/or RO, in the event of occurrence, to mitigate the risk of vision loss [15–17]. Importantly, cumulative post-marketing reporting rates for RV and/or RO cases from the Novartis safety database showed a reduction in cases of reported vision loss associated with these events from its peak in December 2020 to the end of the analysis period in September 2022 (from 5.9 to 4.1 events per 10,000 injections) [18], possibly the result of increased vigilance for events following safety reports and guidance on brolucizumab use.

Patient eyes initiating brolucizumab therapy in the second year after its launch had a significantly lower relative risk of an event than those initiating treatment in the first year after its launch. This is consistent with differences in event incidence in the sub-cohorts (Year 1: 3.1%; Year 2: 2.6%) and may reflect more careful patient selection in the second year compared with the first year after launch as knowledge about brolucizumab increased. Median time to an event was 14 days shorter in the Year 2 than in the Year 1 sub-cohort, which may reflect increased awareness and the importance of early reporting by patients.

The more selective use of brolucizumab is supported by the marked decrease in the number of patients started on brolucizumab in the second year after launch compared with the first year after launch, and there are some interesting differences in patient baseline characteristics between the two sub-cohorts. Patient eyes in the sub-cohort started on brolucizumab during the second year after launch were more likely to be treatment-naive and have a shorter time since nAMD diagnosis than those in the Year 1 sub-cohort. Furthermore, compared with the Year 1 sub-cohort, index VA was lower in the Year 2 sub-cohort. This result might mean that some clinicians are reserving brolucizumab for more difficult-to-treat cases and patients with advanced disease; however, the proportion of treatment-naive eyes was higher in the Year 2 sub-cohort than in the Year 1 sub-cohort, which does not seem consistent with this hypothesis.

The current analysis also showed that the risk of an IOI, RV, and/or RO event was affected by age, sex, and prior anti-VEGF therapy. Eyes from male patients were significantly less likely to experience an event than those from female patients, in line with the earlier IRIS Registry and Komodo database findings [6] and the high proportion of female cases in real-world studies [4, 19, 20]. Furthermore, while the earlier IRIS Registry and Komodo database analysis showed that age and prior anti-VEGF therapy were not associated with an increased risk of any form of IOI and/or RO, the current analysis suggests that treatment-naive eyes were less likely to experience an event than those with prior anti-VEGF therapy and that older age was associated with a reduced risk of an event [6]. These differences could reflect the larger number of patient eyes and longer follow-up period in the current analysis. The Czech study of real-world brolucizumab treatment reported a higher rate of vitritis for patients who switched from prior anti-VEGF therapy than for treatment-naive patients [14]. It was hypothesized that this higher rate may be associated with the cumulative effect of anti-VEGF therapy.

Strengths of the current study are the large sample size and wide coverage of patients with nAMD in the USA, and the relatively long follow-up times, which allow events to be detected up to 2 years after the first brolucizumab injection. Study limitations are the typical difficulties associated with database analyses, such as the reliance on ICD-10 codes for the identification of IOI, RV, and RO events. The findings may also have been affected by the change in characteristics of the patient population over the 2 years following the US launch of brolucizumab. The analysis of VA in patient eyes following an event was limited by the lack of available pre-event and/or follow-up VA data for approximately one-third of these eyes. However, the proportion of eyes with an event that had VA data (66%) was similar to the 70% of patient eyes in the overall study cohort with VA data at index date, suggesting that there was no relationship between having or not having VA data and outcomes.

CONCLUSIONS

To our knowledge, this is the largest study in the world to evaluate the real-world safety outcomes with brolucizumab treatment. Overall, 3.4% of eyes experienced an IOI, RV, and/or RO event, and among those eyes experiencing an event with available VA data, median change in EDTRS score was 0 letters. The study increases our understanding of rates and timing of IOI, RV, and RO events and their effects on vision, and the factors affecting the risk of an event. These results suggest that safety outcomes with brolucizumab in real-world practice may continue to evolve as the understanding of, and experience with, brolucizumab treatment in clinical practice develop over time.

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

Declarations

Conflict of Interest. Marco A. Zarbin: Consultant for Boehringer Ingelheim, EdiGene, Genentech, Inc./Roche, Illuminare, Life Biosciences, Novartis, Perfuse Therapeutics, Seeing Medicines, Smile Biotech, Tamarix Pharmaceuticals, and Tenpoint Therapeutics; holds stock in NVasc. Mathew W. MacCumber: Consultant for Alimera Sciences, Inc., Bausch + Lomb, Genentech, Inc./Roche, IVERIC bio, Novartis Pharma AG, Regeneron Pharmaceuticals, Inc.; research grants from Alimera Sciences, Inc., Apellis Pharmaceutical, Inc., REGENXBIO. Helene Karcher: employee and shareholder of Novartis. Eser Adiguzel: employee and shareholder of Novartis. Andrew Mayhook: contracted employee of Oxford PharmaGenesis. Andrew LaPrise: employee of Verana Health, Inc. Ver L. Bilano: employee of Novartis. Franklin Igwe: employee and shareholder of Novartis. Michael S. Ip: Consultant for Alimera, Allergan, Amgen, Apellis, Clearside Biomedical, Genentech, IVERIC bio, Novartis, Regeneron, and REGENXBIO; research support from 4DMT, Apellis, Biogen, Genentech, IVERIC bio, Lineage Cell Therapeutics, ONL Therapeutics, and REGENXBIO. Charles C. Wykoff: Consultant for 4DMT, AbbVie, Adverum Biotechnologies, Aerie, AGTC, Alcon, Alimera, Allergan, Allgenesis, Alnylam, Annexon Biosciences, Apellis, Arrowhead, Ascidian, Bausch + Lomb, Bayer, Bionic Vision Technologies, Boehringer Ingelheim, Cholgene, Clearside Biomedical, Curacle, Eyebiotech, EyePoint Pharmaceuticals, Foresite, Frontera Therapeutics, Genentech, Gyroscope Therapeutics, IACTA, IVERIC bio, Janssen, Kato Pharma, Kiora, Kodiak Sciences, Kriya Therapeutics, Merck, Nanoscope, Neurotech, NGM Biopharmaceuticals, Notal Vision, Novartis, OccuRx, Ocular Therapeutix, Ocuphire, OcuTerra, OliX, ONL, Opthea, Oxular, Palatin Technologies, Perceive Bio, Perfuse, PolyPhotonix, Ray, RecensMedical, Regeneron, REGENXBIO, Resonance, Roche, Sandoz,

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Ethical Approval. This study complied with the tenets of the Declaration of Helsinki. The analysis was based on de-identified patient data, and this study was reviewed and deemed exempt by the Western-Copernicus Group (WCG) Institutional Review Board (Puyallup, WA, USA) [11]. Informed consent was not required as the analysis was based on de-identified patient data.

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