# Risk of inflammation, retinal vasculitis and retinal occlusion-related events with brolucizumab: post-hoc review of HAWK and HARRIER

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# Risk of Inflammation, Retinal Vasculitis, and Retinal Occlusion–Related Events with Brolucizumab

## *Post Hoc Review of HAWK and HARRIER*

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***Purpose:*** An independent Safety Review Committee (SRC), supported by Novartis Pharma AG, analyzed investigator-reported cases of intraocular inflammation (IOI), endophthalmitis, and retinal arterial occlusion in the phase 3 HAWK and HARRIER trials of brolucizumab versus aflibercept in neovascular age-related macular degeneration (nAMD).

***Design:*** A post hoc analysis of a subset of data from two 2-year, double-masked, multicenter, active-controlled randomized phase 3 trials (NCT02307682, NCT02434328).

***Participants:*** Patients (N = 1817) with untreated, active choroidal neovascularization due to age-related macular degeneration in the study eye were randomized and treated in HAWK/HARRIER. The SRC reviewed data from cases of investigator-reported IOI (60/1088 brolucizumab-treated eyes; 8/729 aflibercept-treated eyes).

***Methods:*** The SRC received details and images (color fundus photography, fluorescein angiography, and OCT) for all investigator-determined cases of IOI, retinal arterial occlusion, and endophthalmitis. Cases were reviewed in detail by ≥2 readers, then adjudicated by the SRC as a group.

***Main Outcome Measures:*** Within this patient subset: incidence of IOI, signs and incidence of retinal vasculitis and/or retinal vascular occlusion, and visual acuity loss; time since first brolucizumab injection to IOI event onset; and frequency of visual acuity loss after brolucizumab injection by time of first IOI event onset.

***Results:*** Fifty brolucizumab-treated eyes were considered to have definite/probable drug-related events within the spectrum of IOI, retinal vasculitis, and/or vascular occlusion. On the basis of these cases, incidence of definite/probable IOI was 4.6% (IOI + vasculitis, 3.3%; IOI + vasculitis + occlusion, 2.1%). There were 8 cases (incidence 0.74%) of at least moderate visual acuity loss (≥15 ETDRS letters) in eyes with IOI (7 in eyes with IOI + vasculitis + occlusion). Of the 8 cases, 5 experienced their first IOI-related event within 3 months of the first brolucizumab injection (increasing to 7/8 within 6 months). Incidence of IOI in aflibercept-treated eyes was 1.1%, with at least moderate visual acuity loss in 0.14%.

***Conclusions:*** This analysis of IOI cases after brolucizumab injection identified signs of retinal vasculitis with or without retinal vascular occlusion and an associated risk of visual acuity loss. The findings will help physicians to evaluate the risks and benefits of brolucizumab treatment for nAMD. *Ophthalmology 2020;■:1–10 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

*Supplemental material available at www.aaojournal.org.*

Choroidal neovascularization is the hallmark of neovascular age-related macular degeneration (nAMD) and a major cause of vision loss.[1,2] Vascular endothelial growth factor (VEGF) is a key mediator of intraocular neovascularization, and intravitreal injection of anti-VEGF agents is the gold standard for treatment of nAMD.[3] Anti-VEGF agents including aflibercept (Eylea; Regeneron), ranibizumab (Lucentis; Genentech), and bevacizumab (Avastin; Genentech) have demonstrated efficacy to reduce vision loss and improve visual acuity in phase 3 clinical trials.[4] Systematic comparison of data from trials of aflibercept, ranibizumab, and bevacizumab in nAMD has revealed little difference between their efficacy and safety profiles.[5,6] These drugs are generally well tolerated. The systemic safety profile is favorable, and rates of cardiovascular or cerebrovascular events are typically low.[7-9] One of the main ocular adverse events (AEs) associated with these agents is intraocular inflammation (IOI).[10]



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In the VIEW studies, for example, in which patients with nAMD were treated with intravitreal ranibizumab or aflibercept, IOI was a predefined AE of interest.[11] Between baseline and 96 weeks, this event was reported in 1.5% of patients receiving ranibizumab and 0.5% to 1.1% of patients in the three aflibercept arms.[11]

Brolucizumab (Beovu, Novartis Pharma AG) is a humanized monoclonal single chain Fv antibody fragment that binds with high affinity to isoforms of VEGF-A and prevents binding of VEGF-A to its receptors VEGF receptor-1 and VEGF receptor-2.[12,13] Brolucizumab was approved for the treatment of nAMD based on data from the phase 3 HAWK and HARRIER clinical trials, which demonstrated that best-corrected visual acuity with brolucizumab (dosed every 12 or 8 weeks after a loading phase with injections at weeks 0, 4, and 8) was noninferior to aflibercept (dosed every 8 weeks after a loading phase with injections at weeks 0, 4, and 8).[14] These visual gains were maintained to week 96.[15] The incidence of serious ocular AEs in the study eye to week 96 was low (<4%) in both trials, and reduced visual acuity was reported as an AE in similar proportions of brolucizumab-treated (6.1%–9.5%) and aflibercept-treated (7.0%–8.1%) patients.[15]

Since the approval of brolucizumab, a number of postmarketing cases of severe visual acuity loss associated with retinal vasculitis and retinal artery occlusion (also described in combination as retinal occlusive vasculitis) have been reported after treatment.[16,17] In February 2020, the American Society of Retinal Specialists indicated that it had "received reports of inflammation which included more than a dozen cases of vasculitis, of which greater than two-thirds were designated as occlusive retinal vasculitis by the reporting providers."[18] On August 28, 2020, postmarketing data indicated that Novartis had received reports of evidence of associated retinal vasculitis and retinal vascular occlusion at a rate of 4.71 per 10 000 brolucizumab injections, while individual events of retinal vasculitis and retinal vascular occlusion were reported at rates of 3.61 and 2.35 per 10 000 injections, respectively.[19] Novartis has concluded that there is a confirmed safety signal of rare AEs of retinal vasculitis and/or retinal vascular occlusion that may result in severe visual acuity loss. Typically, these events occurred in the presence of IOI.[19] To evaluate the relative risks and benefits of brolucizumab with respect to this new safety signal, there is a need to understand the incidence of these signs of retinal vasculitis and/or retinal vascular occlusion.

In patients treated with 6 mg brolucizumab in HAWK and HARRIER, the incidence of IOI reported by the investigators was 4%.[13] The clinical dataset for these investigator-reported cases of IOI provided an opportunity for the Safety Review Committee (SRC) to determine the incidence of definite/probable signs of retinal vasculitis and retinal vascular occlusion, as well as any associated loss of visual acuity, within this subset of patients. We report the findings of this post hoc analysis.

## Methods

### Role of the SRC

The SRC was commissioned by Novartis Pharma AG to provide an independent, standardized assessment of postmarketing reports of patients treated with brolucizumab. The SRC then reviewed cases of IOI, endophthalmitis, and retinal arterial vasculitis in the Phase 3 HAWK and HARRIER trials to determine whether the postmarketing reports represented a new safety signal.

The SRC comprised global retina and uveitis specialists and imaging experts (5 from United States, 3 from Europe) and ophthalmology experts (4 from United States, 2 from Europe) from two separate external Data Monitoring Committees (responsible for monitoring ongoing brolucizumab trials in diabetic macular edema/retinal vein occlusion). An observer from the American Society of Retinal Specialists also attended meetings. Details of the SRC members are available in Table S1 (available at www.aaojournal.org). The SRC had full autonomy with respect to the analysis and assessment of the cases, conclusions formed, and content of this manuscript. Quality checks were performed by Novartis to ensure accuracy.

### Source Data

HAWK and HARRIER were two similarly designed 2-year, double-masked, multicenter, active-controlled, randomized phase 3 clinical trials (NCT02307682, NCT02434328). The studies were conducted in accordance with principles of the Declaration of Helsinki, International Conference on Harmonization E6 Good Clinical Practice Consolidated Guideline, and other regulations as applicable, and were compliant with the Health Insurance Portability and Accountability Act of 1996. All patients provided written informed consent before screening or initiation of any study-related procedures. Protocols were approved by an Independent Ethics Committee/Institutional Review Board. Full details of the trial oversight, randomization, sample size calculations, and inclusion and exclusion criteria have been published previously.[14]

Briefly, 1817 eyes of 1817 participants with untreated nAMD were randomized to intravitreal brolucizumab (3 mg [HAWK only] or 6 mg; n = 1088) or aflibercept (2 mg; n = 729). Loading injections were given at weeks 0, 4, and 8 in both groups, and then brolucizumab injections were administered every 12 weeks (adjusted to 8 weeks if disease activity was present); aflibercept was given every 8 weeks. The primary efficacy end point was mean best-corrected visual acuity change from baseline to week 48. To assess safety, all AEs, serious AEs, ophthalmic examinations (slit-lamp biomicroscopy, intraocular pressure measurements, and fundus examinations), postinjection assessments (including intraocular pressure), clinical laboratory testing (hematology, blood chemistry, and urinalysis), vital sign measurements, and physical examination results were collected. Serum samples were also assessed for systemic brolucizumab levels and antidrug antibodies.

### Review Process

The SRC analyzed investigator-reported cases of IOI, endophthalmitis, and retinal arterial occlusion. The SRC determined whether cases were likely to be drug related and within the spectrum of IOI, retinal vasculitis, and/or retinal vascular occlusion; each was designated as definite, probable, or not. Definitions of events and outcomes were proposed a priori and evolved during the review based on observations made by the SRC. The emphasis

was on inclusion of the investigator-reported cases within the spectrum rather than exclusion from the spectrum; in cases where the findings were equivocal, the SRC always erred on the side of considering the cases drug related and within the spectrum, unless evidence overwhelmingly contradicted this decision.

The SRC also reviewed all cases of investigator-reported IOI, retinal occlusion, and endophthalmitis in the aflibercept cohorts. Treatment assignment was available for all patients reviewed.

Ophthalmic images obtained at standard study and unscheduled visits from before any IOI event and throughout the follow-up visits were reviewed. Images could include color fundus photography (CFP), fluorescein angiography (FA), and OCT, although all images were not available at all visits because this was not required in the protocol. In general, OCT was available at all visits.

Scheduled CFP was performed at screening, week 12, week 48, week 96, and at some unscheduled visits if the investigator chose to obtain them. Images were carefully evaluated to assess retinal arteriolar and venous caliber, and to determine whether there was segmental vascular sheathing and/or vessel emboli. Secondary occlusion manifestations, including cotton wool spots, retinal hemorrhages, and retinal whitening, also were recorded.

Scheduled FA was also performed at screening, week 12, week 48, week 96, and at some unscheduled visits if the investigator chose to obtain them; review included identification of any vascular abnormalities on early and late images. Sequelae of inflammation including disc hyperfluorescence/leakage and vascular leakage were also identified. Images were examined for evidence of vascular occlusion, including nonperfusion, attenuation of arterial and/or venous flow, and choroidal perfusion changes.

Scheduled OCT was performed monthly at each study visit. OCT volume scans were reviewed for each time point before and after the event. OCT scans were evaluated for changes in the vitreous, including increased opacity suggestive of vitreous inflammation, vitreous hyper-reflective spots consistent with vitreous cells, and changes within the retina suggestive of occlusive disease.

### Outcomes

The incidence of definite/probable cases of IOI, IOI with signs of retinal vasculitis, and IOI with signs of retinal vasculitis and retinal vascular occlusion was reported for all eyes treated with brolucizumab in the combined HAWK and HARRIER population, and within subgroups (retinal vasculitis within subgroup with IOI; retinal occlusion within subgroup with IOI + retinal vasculitis). Retinal vasculitis was identified based on imaging findings such as vascular sheathing on CFP and staining or leakage from vessels on FA. Signs of arteriolar occlusion included retinal whitening or emboli on CFP, inner retinal hyperreflectivity on OCT, and boxcarring or arteriolar attenuation and nonperfusion on FA.

The incidence of visual acuity loss within these groups was also reported. Visual acuity was obtained at each visit following a defined protocol using ETDRS charts. At least moderate visual acuity loss was defined as loss of at least 15 ETDRS letters, with severe loss defined as the loss of at least 30 ETDRS letters. Visual acuity loss was based on last available visual acuity measurement versus baseline.

The time from first brolucizumab injection to the first onset of IOI-related event was reported, along with the frequency of visual acuity loss after brolucizumab injection by time of first onset of IOI-related event.

The incidence of IOI and visual acuity loss were also reported for eyes treated with aflibercept in HAWK and HARRIER.

### Statistical Analysis

No formal statistical hypothesis testing was performed as part of this post hoc review of clinical trial data.

## Results

### Analysis Population (Brolucizumab-Treated Eyes)

A total of 1088 eyes of 1088 participants were treated with brolucizumab in the HAWK and HARRIER trials.[14] The SRC reviewed a total of 60 brolucizumab-treated eyes of 60 participants with investigator-reported IOI and/or retinal artery occlusion and/or retinal vasculitis and/or endophthalmitis. Of these 60 cases, 39 had IOI only, 8 had IOI and retinal artery occlusion, 2 had IOI and endophthalmitis, 3 had retinal artery occlusion alone, 1 had perivascular sheathing, and 7 had endophthalmitis alone. An additional 3 cases were reviewed from a HAWK extension study but were not included in the incidence calculations because of differences in study design.

In the 60 eyes, 28 investigator-reported events were categorized as "definite," and 22 investigator-reported events were categorized as "probable," with regard to being both drug related and within the spectrum. The remaining 10 investigator-reported events were categorized as "not drug related, not in spectrum." The reasons eyes were excluded included endophthalmitis (culture-proven or per investigator; n = 4), presence of inflammation at baseline (n = 2), retinal artery occlusion without IOI (n = 1), unexplained inflammation after cataract surgery (n = 1), baseline leakage at disc (n = 1), and macular hole (n = 1). All data for brolucizumab-treated eyes presented in this article relate to the 50 eyes with events categorized as definite or probable.

### Incidence of Definite/Probable IOI, Retinal Vasculitis, and Retinal Vascular Occlusion Events (Brolucizumab-Treated Eyes)

Of the 50 eyes with definite/probable IOI events, 36 showed signs of retinal vasculitis. In turn, 23 of these cases showed signs of retinal vasculitis + retinal occlusion. The incidence rates of these events in the total HAWK and HARRIER population, and within each subgroup are shown in Figure 1. In HAWK and HARRIER, the incidence of definite/probable IOI was 4.6%, IOI + retinal vasculitis was 3.3%, and IOI + retinal vasculitis + retinal occlusion was 2.1%. In eyes with definite/probable IOI (n = 50), the incidence of retinal vasculitis was 72.0%; in eyes with IOI + retinal vasculitis (n = 36), the incidence of retinal occlusion was 63.9%. Representative images of typical cases are available in Figure S1 (available at www.aaojournal.org).

### Risk of Visual Acuity Loss Associated with IOI ± Retinal Vasculitis ± Retinal Vascular Occlusion Events

There were 8 cases of at least moderate visual acuity loss (≥15 ETDRS letters), 5 of which were severe (≥30 ETDRS letters), among eyes with definite/probable IOI (Table 1). All but 1 of these cases occurred in eyes with definite/probable IOI + retinal vasculitis + retinal occlusion. The other case (moderate visual acuity loss) occurred in an eye with definite/probable IOI + retinal vasculitis but without retinal occlusion.

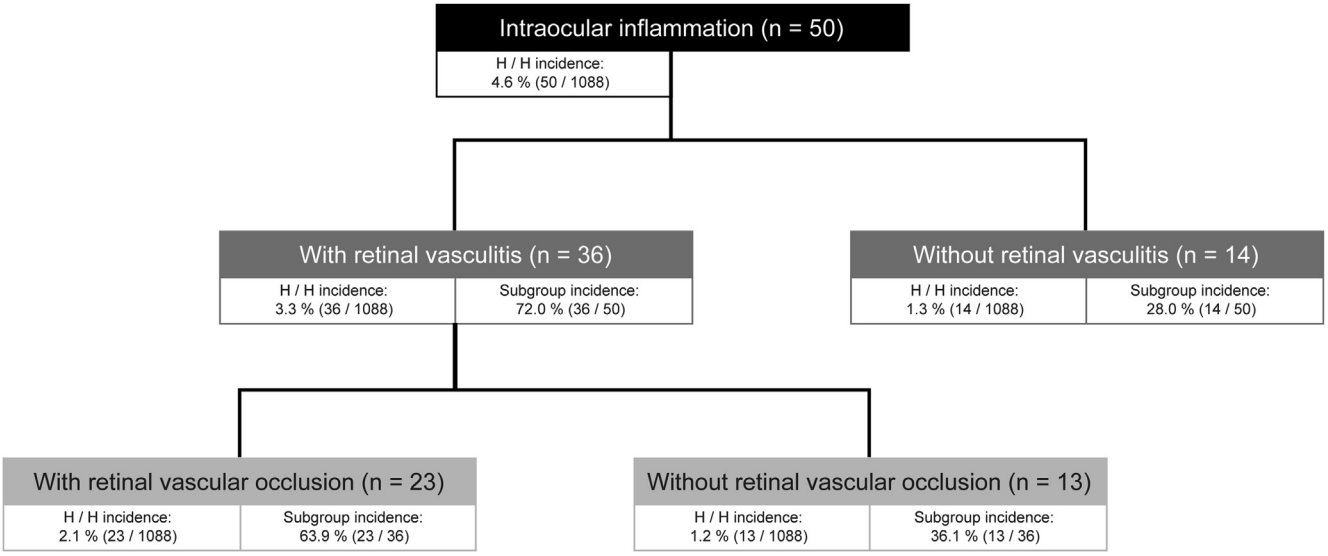



**Figure 1.** Incidence of intraocular inflammation (IOI), IOI with retinal vasculitis, and IOI with retinal vasculitis and retinal occlusion: definite and probable cases combined (brolucizumab-treated eyes). Numbers relate to all cases categorized as "definitely drug related; within spectrum of IOI, retinal vasculitis and/or retinal vascular occlusion" or "probably drug-related; probably in the spectrum." HAWK and HARRIER incidence based on all 1088 patients analyzed from HAWK and HARRIER studies. Subgroup incidence based on subgroup with IOI (n = 50) or IOI with retinal vasculitis (n = 36), as appropriate. H/H = HAWK and HARRIER.

### Timing of Definite/Probable IOI, Retinal Vasculitis, and Retinal Vascular Occlusion and Visual Acuity Loss Events (Brolucizumab-Treated Eyes)

The median (range) number of days from the last injection to the onset of event was 25.5 (1−91) for IOI, 22 (1−49) for IOI + retinal vasculitis, and 25 (3−49) for IOI + retinal vasculitis + retinal occlusion. The frequency distribution of time since first injection for definite/probable IOI-related event is shown in Figure 2, and time to event curves are shown in Figure 3. Approximately three quarters of cases of each event occurred within the initial 6 months after the first injection. Approximately half of cases occurred within the first 3 months (IOI, 24/50 [48.0%]; IOI + retinal vasculitis, 18/36 [50.0%]; IOI + retinal vasculitis + retinal occlusion, 13/23 [56.5%]). There were 8 cases of definite/probable IOI (5 of these with definite/probable retinal vasculitis + retinal occlusion) that occurred in patients who had received only 1 injection.

The frequency distribution of "at least moderate visual acuity loss likely due to the inflammation event" by time of first onset of definite/probable IOI-related event since first injection is shown in Figure 4A. Among eyes with at least moderate visual acuity loss likely due to the inflammation event, more than one half of the first investigator-reported IOI-related events occurred within 3 months of the first injection (IOI, 5/8 [62.5%]; IOI + retinal vasculitis, 5/8 [62.5%]; IOI + retinal vasculitis + retinal occlusion, 4/7 [57.1%]). A similar pattern was observed for cases of "severe visual acuity loss likely due to the inflammation event" (IOI, 3/5 [60.0%]; IOI + retinal vasculitis, 3/5 [60.0%]; IOI + retinal vasculitis + retinal occlusion, 3/5 [60.0%] associated with events occurring in the first 3 months; Fig 4B).

### Analysis of Eyes Treated with Aflibercept

In HAWK and HARRIER, 729 eyes of 729 participants were treated with aflibercept.[14] A total of 8 eyes with IOI were identified by investigators from the aflibercept groups; the overall incidence was 1.1% (8/729). The overall risk of at least moderate visual acuity loss in eyes with IOI in the aflibercept arms of the HAWK and HARRIER trials was 0.14% (1/729), with a risk of 12.5% (1/8) in the affected subpopulation.

### Overall Loss of Visual Acuity in the HAWK and HARRIER Studies

The overall rates of moderate or severe visual acuity loss, including visual acuity loss associated with definite/probable IOI, retinal vasculitis, and/or retinal occlusion, were 7.4% (81/1088) and 7.7% (56/729) in brolucizumab- and aflibercept-treated eyes, respectively.

## Discussion

In response to postmarketing reports of severe vision loss, retinal arterial/vascular occlusion, and vasculitis in patients treated with brolucizumab, this analysis evaluated rates of inflammatory events in the investigator-reported cases of IOI in the phase 3 HAWK and HARRIER clinical trials. In HAWK and HARRIER, Medical Dictionary for Regulatory Activities (MedDRA) terms were used to code AEs based on investigator reports. Codes for retinal vasculitis and retinal occlusive vasculitis are not included in the MedDRA terms. Thus, in some cases, the investigator chose IOI terms, and in others, retinal artery or vein occlusion; this made discovering retinal occlusive vasculitis difficult.

In the current post hoc analysis, the committee performed extensive and thorough review of potential cases to provide clinical case identification and description without regard to the MedDRA terms. Based on the 60 investigator-reported cases, among which 50 were classified by the SRC as definitely/probably within the spectrum of IOI, retinal vasculitis, and/or retinal vascular occlusion, the incidence of IOI in brolucizumab-treated eyes in HAWK and HARRIER

Table 1. Cases of Visual Acuity Loss by Intraocular Inflammation, Retinal Vasculitis, and Retinal Occlusion Grouping: Definite and Probable Cases Combined (Brolucizumab-Treated Eyes)

| Visual Acuity Loss Event | No. of Cases | Incidence in HAWK and HARRIER* | | Incidence in Subgroup with Event† | |
|---|---|---|---|---|---|
| | | *n/N* | % | *n/N* | % |
| Visual acuity loss, cases with IOI | | | | | |
| At least moderate | 8 | 8/1088 | 0.74% | 8/50 | 16.0% |
| Severe | 5 | 5/1088 | 0.46% | 5/50 | 10.0% |
| Visual acuity loss, cases with IOI without retinal vasculitis | | | | | |
| At least moderate | 0 | 0/1088 | 0.0% | 0/14 | 0.0% |
| Severe | 0 | 0/1088 | 0.0% | 0/14 | 0.0% |
| Visual acuity loss, cases with IOI + retinal vasculitis | | | | | |
| At least moderate | 8 | 8/1088 | 0.74% | 8/36 | 22.2% |
| Severe | 5 | 5/1088 | 0.46% | 5/36 | 13.9% |
| Visual acuity loss, cases with IOI + retinal vasculitis without retinal occlusion | | | | | |
| At least moderate | 1 | 1/1088 | 0.09% | 1/13 | 7.69% |
| Severe | 0 | 0/1088 | 0.0% | 0/13 | 0.0% |
| Visual acuity loss, cases with IOI + retinal vasculitis + retinal occlusion | | | | | |
| At least moderate | 7 | 7/1088 | 0.64% | 7/23 | 30.4% |
| Severe | 5 | 5/1088 | 0.46% | 5/23 | 21.7% |

IOI = intraocular inflammation.
Numbers relate to all cases categorized as "definitely drug related; within spectrum of IOI, retinal vasculitis and/or retinal vascular occlusion" or "probably drug-related; probably in the spectrum."
At least moderate visual acuity loss defined as ≥15 ETDRS letter loss; severe visual acuity loss as ≥30 ETDRS letter loss.
*HAWK and HARRIER incidence based on rate of visual acuity loss due to the adverse event (AE) in all 1088 patients analyzed in HAWK/HARRIER.
†Subgroup incidence based on rate of visual acuity loss in patients for whom the AE is present.

can be interpreted as at least 4.6% (vs. 1.1% for aflibercept-treated eyes). The observed incidence of definite/probable IOI with signs of retinal vasculitis was 3.3% and definite/probable IOI with signs of retinal vasculitis and retinal vascular occlusion was 2.1% in brolucizumab-treated eyes. Additional cases may have been identified if the SRC had

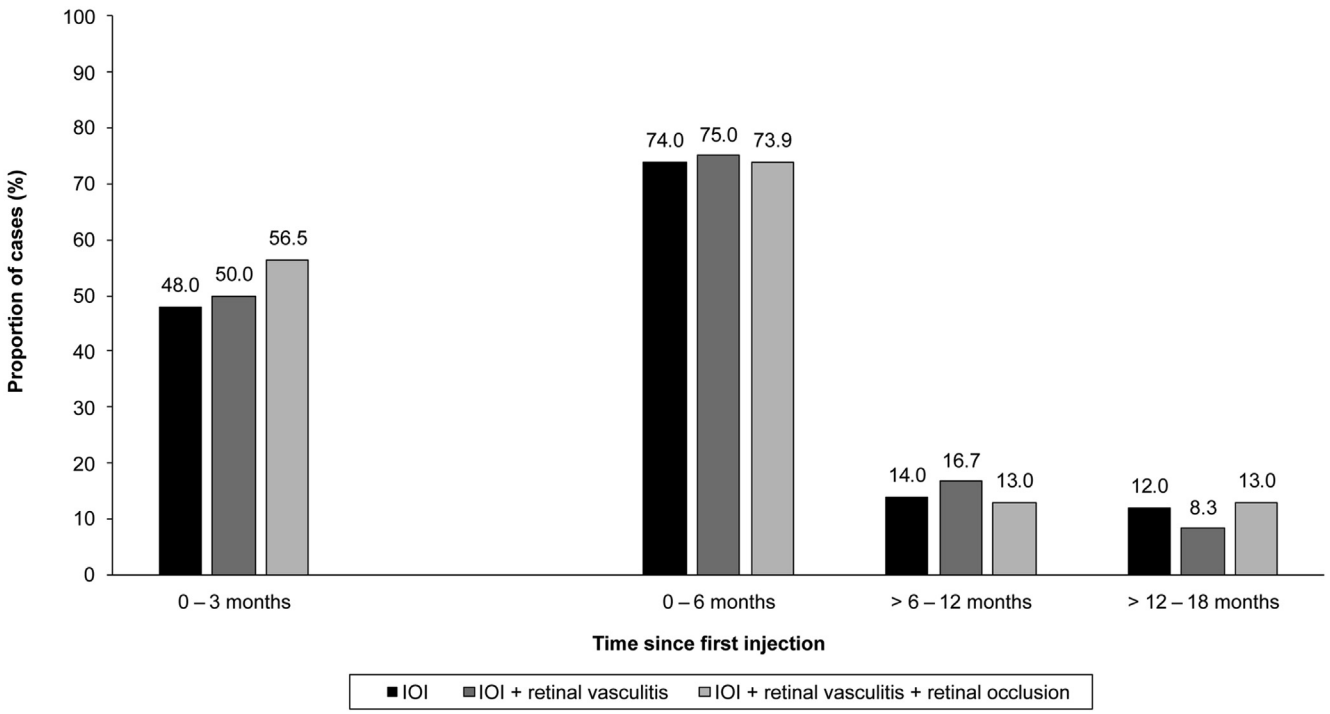
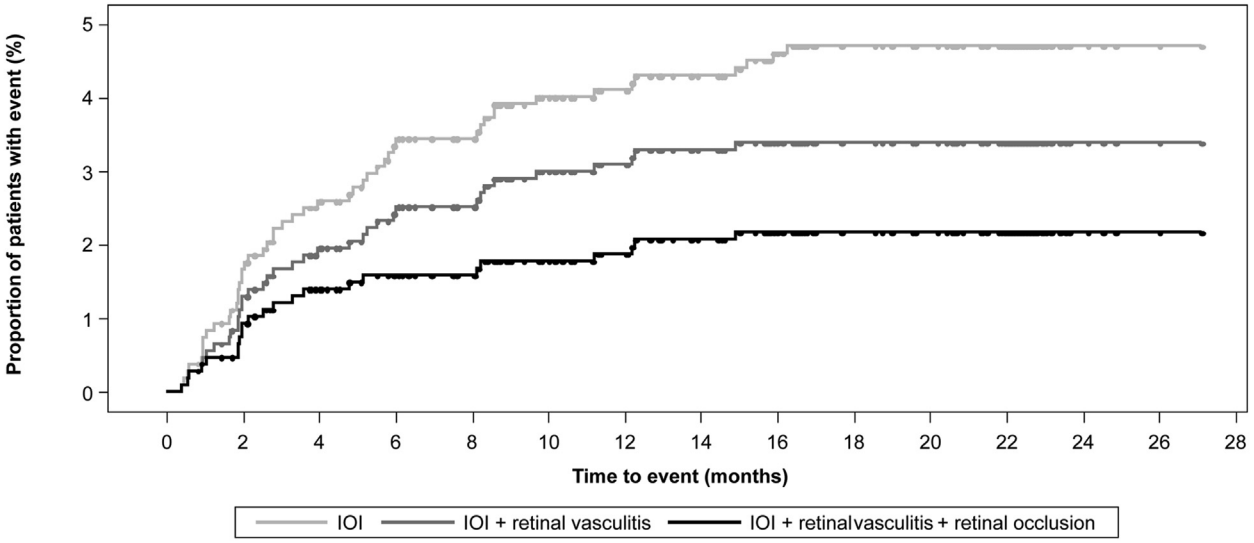



**Figure 2.** Frequency distribution of time since first injection (months) by onset category: definite and probable cases combined (brolucizumab-treated eyes). Note that categories are not mutually exclusive. IOI + retinal vasculitis + retinal occlusion is a subset of IOI + retinal vasculitis, which is a subset of IOI. IOI = intraocular inflammation.




**Number of patients at risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IOI | 1088 | 1067 | 1047 | 1029 | 1020 | 998 | 985 | 968 | 952 | 938 | 933 | 910 | 5 | 2 | 0 |
| IOI + retinal vasculitis | 1088 | 1070 | 1053 | 1037 | 1028 | 1006 | 993 | 976 | 962 | 949 | 944 | 921 | 5 | 2 | 0 |
| IOI + retinal vasculitis + retinal occlusion | 1088 | 1074 | 1059 | 1046 | 1037 | 1017 | 1004 | 987 | 973 | 960 | 955 | 932 | 5 | 2 | 0 |

**Figure 3.** Time since first injection to first IOI-related event (Kaplan–Meier plot; brolucizumab-treated eyes). Note that categories are not mutually exclusive. IOI + retinal vasculitis + retinal occlusion is a subset of IOI + retinal vasculitis, which is a subset of IOI. AE = adverse event; IOI = intraocular inflammation.

applied the conservative review to all patients in the two studies. The purpose of this analysis was to assess these events in brolucizumab-treated eyes and not to compare them with aflibercept. Cases of IOI in aflibercept-treated eyes were not fully analyzed; therefore, it is inappropriate to draw conclusions between the two treatments in this case.

Uncontrolled postmarketing data, which may be derived from cases in treatment-naïve patients as well as patients switched from other anti-VEGF treatments, are subject to limitations, including inconsistencies in diagnostic criteria, incomplete documentation, and considerable possibility of underreporting. The findings of this analysis represent a valuable resource on which physicians may base decisions relating to the risks and benefits of brolucizumab in patients with treatment-naïve nAMD. A direct comparison of the reported incidence rates with those identified in the postmarketing setting is not appropriate. However, the findings of the current analysis, together with the published efficacy and safety data from HAWK and HARRIER, can be used by clinicians to make informed decisions regarding the use of brolucizumab in their patients with nAMD. To help put the findings into context, the incidence of inflammatory events in other studies of anti-VEGF agents may be considered, although it is important to acknowledge differences in methodology used to identify cases. In the CATT trials, endophthalmitis occurred in the study eye of 0.7% of patients treated with monthly ranibizumab (plus an additional 0.3% with pseudoendophthalmitis) and 1.4% of patients treated with monthly bevacizumab.[20] A wide range of IOI rates after bevacizumab treatment has been reported in single-center studies (0.3% to 14.3%).[10] A large retrospective, claims-based analysis (N = 432 794 injections) reported that severe IOI occurred at a rate of 1.06/1000 aflibercept injections and 0.64/1000 ranibizumab injections.[21] A recent review of data from the postmarketing aflibercept Global Safety Database indicated that retinal arterial occlusion, vasculitis, or severe vision loss occurred at a rate of 0.9 per 10 000 aflibercept injections.[22]

Three-quarters of the inflammation events were first observed within 6 months after initiation of brolucizumab, although some occurred between 12 and 18 months after the treatment. It is important for clinicians to be aware that although the risk of inflammation is highest soon after injections are given, ongoing vigilance is vital because episodes may still occur more than 1 year postinjection. Notably, patients whose first IOI-related event occurred more than 12 months after the first injection had no reported vision loss at the end of the study.

In this post hoc analysis, the overall incidence of at least moderate visual acuity loss associated with IOI was <1% in both brolucizumab- and aflibercept-treated eyes. In brolucizumab-treated eyes with definite/probable IOI, the risk of at least moderate visual acuity loss was 22.2% in eyes with signs of retinal vasculitis and 30.4% in eyes with signs of retinal vasculitis + retinal occlusion. In brolucizumab-treated eyes with definite/probable IOI, the risk of severe visual acuity loss was 13.9% in eyes with signs of retinal vasculitis and 21.7% in eyes with signs of retinal vasculitis + retinal occlusion. Despite these data,

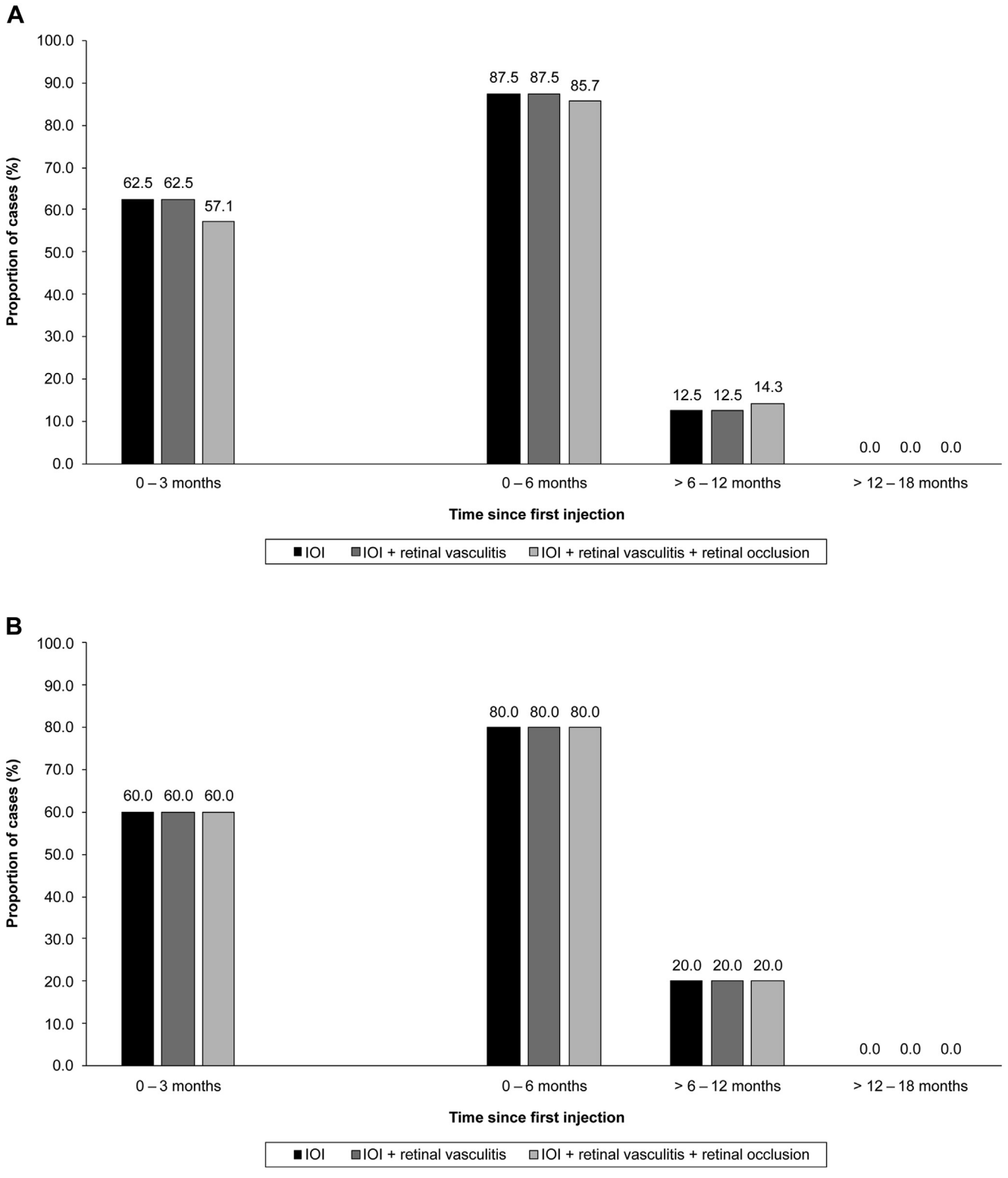



**Figure 4.** Frequency distribution of cases of **(A)** at least moderate or **(B)** severe visual acuity loss likely due to the inflammation event by time of onset of first IOI-related event since first injection (brolucizumab-treated eyes). Note that categories are not mutually exclusive. IOI + retinal vasculitis + retinal occlusion is a subset of IOI + retinal vasculitis, which is a subset of IOI. IOI = intraocular inflammation.

overall rates of moderate or severe visual acuity loss (including that associated with definite/probable IOI, retinal vasculitis and/or retinal occlusion) were similar for brolucizumab and aflibercept (7.4% and 7.7%, respectively). The time course and severity of visual acuity loss may be sensitive to whether signs of retinal vasculitis and/or retinal vascular occlusion are present with IOI. It has been demonstrated that some aflibercept-treated eyes benefit from a monthly dosing interval.[23] Certain eyes from either treatment group in HAWK and HARRIER might have experienced better preservation of visual acuity if their dosing frequency had been increased.

The SRC adopted a thorough, discussion-based approach to review the cases that ensured generalizability of these findings to clinical practice. The study population was sufficiently large to support analysis of the incidence of uncommon events. Although the source population was defined by the enrolment criteria of HAWK and HARRIER, analysis of cases was performed using clinically relevant methodology. However, the analysis was subject to a number of limitations. As described, the SRC applied a cautious approach to the analysis and included both definite and probable cases of IOI/retinal vasculitis/retinal vascular occlusion in their calculations of incidence. The inclusion of "questionable" cases must be taken into consideration when interpreting the incidence rates presented. The SRC's retrospective review depended on the imaging available for analysis. Color fundus photography was only obtained at limited intervals and typically included 30-degree field posterior pole images, which limited the assessment of the peripheral retina. Likewise, fluorescein angiograms were usually not widefield and limited in number, preventing the assessment of peripheral vasculitis signs and retinal blood flow. The SRC only reviewed cases in which IOI, endophthalmitis, and retinal arterial occlusion had been reported by investigators; these cases tended to have more imaging available around the time of the event. The actual event rate may have been higher than reported by the investigators, particularly if some of the cases were minimally symptomatic or asymptomatic. This analysis was limited to treatment-naïve patients as per HAWK and HARRIER inclusion criteria; no conclusions can be drawn relating to the incidence of these AEs in patients with a history of anti-VEGF therapy. Finally, the findings and their description will have been affected by the premature study discontinuation of some patients, and it is important to recognize that no formal statistical comparisons were performed for this post hoc analysis.

Based on the findings of this analysis, we encourage vigilance in practice, with active surveillance and prompt reporting of cases of IOI, retinal vasculitis, and retinal occlusion. Routine monitoring should be more comprehensive than that typically performed in clinical practice, incorporating slit-lamp examination and ophthalmoscopy combined with fundus imaging (if inflammation is suspected). Careful examination of fundus imaging in some cases revealed subtle vasculitis and/or occlusive disease that could not be appreciated on dilated fundus examination. OCT scans should be reviewed for signs of inflammation. A full description of the analysis of images by the SRC will be published in due course. Brolucizumab is contraindicated in patients with active IOI.[12,13] If inflammation is detected, injections should cease, widefield FA or FA with peripheral sweeps should be performed, and systemic and/or local corticosteroid treatment considered. Analysis suggested there may be an association between inflammatory events and boosted or emergent antidrug antibodies; this observation is under further evaluation by Novartis.

In conclusion, this rigorous analysis of cases of definite/probable IOI that occurred in the phase 3 HAWK and HARRIER clinical trials identified a number of cases with signs of retinal vasculitis with or without signs of retinal vascular occlusion, and such events were associated with increased risk of visual acuity loss. It is critical that treating physicians monitor appropriately for this safety signal during brolucizumab treatment. These findings will help physicians to make informed decisions when balancing these risks against the demonstrated efficacy and durability of brolucizumab in nAMD.

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## Footnotes and Disclosures

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Abbreviations and Acronyms:
**AE** = adverse event; **CFP** = color fundus photography; **FA** = fluorescein angiography; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IOI** = intraocular inflammation; **MedDRA** = Medical Dictionary for Regulatory Activities; **nAMD** = neovascular age-related macular degeneration; **SRC** = Safety Review Committee; **VEGF** = vascular endothelial growth factor.

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