Clinical Characteristics and Outcomes of Eyes with Intraocular Inflammation after Brolucizumab: Post Hoc Analysis of HAWK and HARRIER

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Purpose: This analysis of the pivotal phase 3 HAWK and HARRIER trials aimed to provide insights on the timing of presentation, management, and outcomes of intraocular inflammation (IOI)-related adverse events (AEs), as reported by investigators in these trials.

Design: Post hoc analysis of investigator-reported IOI-related AEs in HAWK and HARRIER.

Participants: Of 1088 brolucizumab-treated eyes (3 or 6 mg), 49 eyes demonstrated at least 1 IOI-related AE and were included in this analysis.

Methods: Reports of IOI-related AEs were analyzed and descriptive statistics were provided for outcome measures.

Main Outcome Measures: Incidence and description of eyes with IOI-related AEs, timing of presentation, management, clinical outcomes, and brolucizumab treatment after the first IOI-related AE.

Results: Seventy IOI-related AEs were reported in 49 eyes. Before the onset of first IOI-related AE, eyes received a mean ± standard deviation (SD) of 3.9 ± 2.2 brolucizumab injections. Median time to first IOI-related AE from the last administered brolucizumab injection was 18.0 days (interquartile range, 4.0–29.0 days). Of the 70 AEs, 61 (87.1%) were treated, most with topical corticosteroids; systemic and intraocular corticosteroids were used for 3 AEs each. Overall, inflammation resolved completely in 39 eyes (79.6%), resolved with sequelae in 5 eyes (10.2%), and did not resolve in 5 eyes (10.2%) by end-of-study (EOS). Overall, the mean ± SD best-corrected visual acuity (BCVA) change from baseline to EOS, before AE to the lowest BCVA in 3 months after AE, and from before AE to EOS were 0.84 ± 20.6, −16.31 ± 17.6, and −0.22 ± 18.9 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, respectively. Of the 36 eyes (73.5%) that continued with brolucizumab therapy after the first IOI-related AE, 24 completed the trials and 12 discontinued; mean ± SD BCVA change in these eyes was 2.6 ± 17.6, 7.8 ± 13.2, and −7.7 ± 21.3 ETDRS letters, respectively, from baseline to EOS. The remaining 13 eyes (26.5%) were not treated with brolucizumab after first IOI-related AE and showed a mean ± SD BCVA change of −10.4 ± 25.5 ETDRS letters from baseline to EOS.

Conclusions: Findings of this analysis highlight the need for continued vigilance and monitoring for any signs of IOI-related events in patients receiving brolucizumab. Ophthalmology Retina 2021; ●1–12 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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Intravitreal injection of anti–vascular endothelial growth factor (VEGF) agents has revolutionized the treatment of neovascular age-related macular degeneration (nAMD) and reduced the risk of vision loss resulting from nAMD.1–2 Brolucizumab 6 mg has been approved for the treatment of nAMD based on the results of the pivotal phase 3 HAWK and HARRIER trials, where brolucizumab 6 mg was noninferior to aflibercept 2 mg based on best-corrected visual acuity (BCVA) outcomes at week 48 (primary end point).3–5 Brolucizumab demonstrated an overall well-tolerated safety profile over 96 weeks in these trials. Intraocular inflammation (IOI) was reported in 4% of eyes treated with brolucizumab 6 mg compared with 1% of those treated with aflibercept 2 mg.5,5

After approval of brolucizumab 6 mg for the treatment of nAMD by the Food and Drug Administration in October 2019, reports appeared of retinal vasculitis, retinal artery occlusion (RAO), or both accompanied by IOI with
intravitreal injections of brolucizumab. Based on post-marketing reports received by Novartis, as of March 30, 2021, the incidence rate of retinal vasculitis, retinal vascular occlusion, or both is estimated to be 15.6 cases per 10,000 brolucizumab injections, with an associated risk of vision loss of 5.5 cases per 10,000 injections. However, because postmarketing data depend on physician reporting and may underestimate events, Novartis commissioned an external safety review committee (SRC) to further define the incidence of these events and the risk of vision loss. Based on an unmasked, independent reassessment of investigator-reported adverse events (AEs) of IOI, endophthalmitis, and RAO in brolucizumab-treated eyes from the HAWK and HARRIER trials, the SRC concluded that the incidence of IOI was 4.6%, IOI plus retinal vasculitis was 3.3%, and IOI plus retinal vasculitis plus retinal vascular occlusion was 2.1%; the overall incidence of at least moderate visual acuity (VA) loss associated with IOI was less than 1%. Based on these findings, a safety signal of infrequent AEs of retinal vasculitis, retinal vascular occlusion, or both that may result in severe vision loss was confirmed. These events typically occurred in the presence of IOI. The brolucizumab label has been updated to include this safety information and approved by major regulatory authorities. Because the HAWK and HARRIER trials remain the most complete datasets for brolucizumab in nAMD to date, the purpose of this post hoc analysis was to report on the timing of presentation, management, and outcomes of the investigator-reported IOI-related AEs during these trials.

Methods
This was a post hoc analysis of investigator-reported cases of IOI in patients from the HAWK (ClinicalTrials.gov identifier, NCT02307682) and HARRIER (ClinicalTrials.gov identifier, NCT02434328) trials, 2 similarly designed, 96-week, randomized, double-masked, phase 3 multicenter trials. These trials were conducted in accordance with the tenets of the Declaration of Helsinki, the International Conference on Harmonization E6 Good Clinical Practice consolidated guidelines, and other regulations as applicable and complied with the Health Insurance Portability and Accountability Act of 1996. All trial participants provided written informed consent, and independent ethics committee or institutional review board approval was obtained for these trials. Details of the design and 48- and 96-week outcomes of the trials have been published previously.

In brief, 1,817 eyes with treatment-naive nAMD from 1,817 participants were randomized to receive intravitreal brolucizumab (3 mg [HAWK only] or 6 mg; n = 1,088) or aflibercept (2 mg; n = 729). Loading injections were administered at weeks 0, 4, and 8 for all treatment arms, followed by brolucizumab injection every 12 weeks (with an option to adjust to every 8 weeks if disease activity was identified at predefined visits); aflibercept was given in a fixed every-8-weeks regimen. All participants underwent protocol-defined scheduled visits every 4 weeks through to week 96. In addition, participants could undertake an unscheduled visit. The primary efficacy end point was noninferiority of brolucizumab to aflibercept in the mean change in BCVA from baseline to 48 weeks.

Safety outcomes included the incidence of ocular and nonocular AEs and serious AEs over 96 weeks. Adverse events were identified at scheduled study visits (as defined by the protocols) as well as at unscheduled visits. All AEs were reported by the investigators based on their clinical judgment and according to International Conference on Harmonization E6 Good Clinical Practice guidelines. The AEs were listed ad verbatim as reported by the investigators, mapped to the closest term in the Medical Dictionary for Regulatory Activities (MedDRA; version 20.1) and then coded automatically to 1 specific preferred term. The use of MedDRA is required by regulatory authorities and scientific societies for controlled studies to report AEs in a standardized way by using clinically validated medical terminology across regulatory regions.

Post Hoc Analysis
This post hoc analysis included investigator-reported cases of IOI-related AEs in brolucizumab-treated (3 mg and 6 mg) eyes in the combined HAWK and HARRIER trial population. Intraocular inflammation-related AEs in the aflibercept 2-mg arm were not included in this analysis. The following MedDRA preferred terms were considered to be IOI-related AEs: anterior chamber cell, anterior chamber flare, anterior chamber inflammation, choriorretinitis, eye inflammation, iridocyclitis, iritis, keratic precipitates, retinal vasculitis, uveitis, and vitritis. Of note, no investigator-reported AEs were coded as occlusive vasculitis in the HAWK and HARRIER trials because these terms were not included in MedDRA version 20.1. Investigator-reported cases of RAO and endophthalmitis were excluded from this post hoc analysis. However, their clinical presentation, management, and outcomes are described briefly.

Outcome Measures
Incidence and Severity of Intraocular Inflammation-Related Adverse Events. The incidence of IOI-related AEs in brolucizumab-treated eyes and the baseline characteristics of these eyes were assessed. The severity of the AEs, as determined by the investigators based on their clinical judgment, was reported. Adverse events in HAWK and HARRIER were classified as mild, moderate, or severe based on the following definitions in the trial protocols:

1. Mild: when the patient is aware of the AE but can easily tolerate the sign or symptom.
2. Moderate: if the sign or symptom results in discomfort significant enough to cause interference with the patient’s usual activities.
3. Severe: if the sign or symptom is incapacitating and results in the inability of the patient to work or engage in their usual activities.

Number of Brolucizumab Injections and Timing and Duration of Intraocular Inflammation-Related Adverse Events. The number of brolucizumab injections given before the first IOI-related AE and the time to onset of the first IOI-related AE from the study baseline and from the last administered brolucizumab injection were assessed. The number of AEs reported at scheduled and unscheduled study visits was also determined.

The duration of the AE was reported from the start to the end of the event, where the end date was determined by the investigator depending on the outcome of the event. For AEs that “recovered/resolved” or “recovered/resolved with sequelae,” the date of the event resolution was considered as the end date. For AEs that did not recover or resolve, the end date was considered (for the purpose of this analysis) as the date of patient withdrawal from the study or the end of study, whichever was applicable; however, this did not reflect the end of the AE.
Management of Intraocular Inflammation-Related Adverse Events and Outcomes. The management of IOI-related AEs during the conduct of the trials was described. The AEs were managed based on the investigator’s clinical expertise; no specific treatment regimen was defined in the trial protocols. The type and method of treatment given and the time of treatment initiation were reported.

The outcomes of IOI-related AEs were determined based on the investigator’s clinical decision. For eyes with more than 1 AE, the event with the worst outcome was considered for the analysis. The outcomes were defined in 1 of the following 3 categories:

1. Recovered/resolved: the event is completely resolved without any secondary consequences.
2. Recovered/resolved with sequelae: the existing event is resolved, but the patient experiences another event as a consequence of the first AE. In this context, recovered or resolved with sequelae was defined as worsening severity of an existing AE (for example, a mild AE worsening in severity to a moderate AE was recorded as resolved with sequelae for the mild event) or when the existing AE was considered related to a subsequently reported AE.
3. Not recovered/not resolved: the event is not resolved, is persisting (at the same level of severity), and no improvement is observed.

Best-Corrected Visual Acuity Outcomes. Best-corrected visual acuity was measured by protocol-defined refraction testing using standardized Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Change in BCVA letters from baseline to the end of study (96 weeks), overall and by severity of AEs, was reported using last observation carried forward imputation for missing values. To understand the impact of IOI-related AEs on visual outcomes, BCVA change from before the event to the lowest BCVA in the 3 months after the event was assessed. The BCVA change from before the event to the end of study was also evaluated. Eyes experiencing more than 1 AE were counted under maximum severity as moderate. Finally, the proportion of eyes that gained or lost 15 ETDRS letters or more and 30 ETDRS letters or more was also reported.

Treatment Continuation with Brolucizumab after the First Intraocular Inflammation-Related Adverse Event. The proportion of eyes that continued brolucizumab treatment after the first IOI-related AE was reported. Change in BCVA from baseline to the end of study was evaluated for these eyes.

Description of Investigator-Reported Intraocular Inflammation-Related Adverse Events from the Afiblercept Arm

The incidence, severity, and outcomes (recovery and VA) of investigator-reported IOI-related AEs in eyes treated with aflibercept in the HAWK and HARRIER trials were reported.

Statistical Analysis

In this post hoc review of HAWK and HARRIER clinical trial data, descriptive summary statistics were provided for all outcome measures. No significance testing was performed. The last observation carried forward imputation method was used for missing values.

Results

Incidence and Severity of Intraocular Inflammation-Related Adverse Events in Brolucizumab-Treated Eyes

Of the 1088 brolucizumab-treated eyes (3-mg and 6-mg groups combined) in HAWK and HARRIER, 49 eyes (from 49 patients [4.5%]) experienced at least 1 investigator-reported IOI-related AE. Of these 49 eyes, 35 eyes (71.4%) had 1 AE, whereas 14 eyes (28.6%) had 2 or more AEs (2 AEs, n = 10; 3 AEs, n = 1; 4 AEs, n = 1).

Figure 1. Bar graph showing the frequency distribution of eyes based on the number of brolucizumab injections given before the onset of the first intraocular inflammation (IOI)-related adverse event (AE).
n = 3) reported on separate visits. No reports were made of multiple IOI events at a single visit during the course of the trials. The mean ± standard deviation (SD) age of patients was 74 ± 9.1 years, and 36 patients (73.5%) were women. The demographics of these 49 patients are detailed in Table S1 (available at www.ophthalmologyretina.org). Among these 49 eyes, a total of 70 IOI-related AEs coded to a specific MedDRA preferred term were reported, as detailed in Table S2 (available at www.ophthalmologyretina.org). Of these 70 AEs, 38 (54.3%) were classified as mild, 28 (40.0%) were classified as moderate, and 4 (5.7%) were classified as severe by the investigators during the trial.

Figure 2. Kaplan-Meier graphs showing time to onset of the first or the most severe intraocular inflammation (IOI)-related adverse event (AE)* from (A) baseline and (B) the last brolucizumab injection, overall and by severity. *In 14 patients who had more than 1 AE, the time to onset of the most severe AE was considered.
Number of Brolucizumab Injections and Timing and Duration of Intraocular Inflammation-Related Adverse Events. The mean ± SD and median number of brolucizumab injections before the onset of the first IOI-related AE were 3.9 ± 2.21 and 3.0 (25th–75th percentile, 2.0–5.0), respectively. Based on the severity of the first IOI-related AE, the respective mean ± SD and median number of brolucizumab injections given before the onset of the event were 4.0 ± 2.38 and 3.0 (25th–75th percentile, 2.0–5.0) for mild, 3.8 ± 2.20 and 3.0 (IQR, 2.0–5.0) for moderate, and 3.7 ± 0.58 and 4.0 (25th–75th percentile, 3.0–4.0) for severe AEs. The frequency distribution of eyes based on the number of brolucizumab injections administered before the onset of the first IOI-related AE is presented in Figure 1.

The mean ± SD and median time to onset of the first IOI-related event from baseline were 165.6 ± 153.6 days and 100.0 days (25th–75th percentile, 56.0–249.0 days; range, 1–507 days), respectively, and from the last brolucizumab injection were 20.3 ± 17.18 days and 18.0 days (25th–75th percentile, 4.0–29.0 days; range, 1–72 days), respectively. Time-to-event curves are shown in Figure 2. Of the 70 IOI-related AEs, investigators reported 50 AEs at unscheduled visits (11 mild, 6 moderate, and 3 severe AEs). Two events (22.2%) were reported by the investigators as not resolved by the end of study. It is notable that 9 of the 70 AEs (12.9%; 8 mild and 1 moderate AE) were observed and no treatment was administered; 7 of these events resolved and 2 resolved with sequelae.

Among the 61 treated IOI-related AEs, 52 events (85.3%) were reported by the investigators as resolved, 4 events (6.5%) were reported by the investigators as resolved with sequelae, and 5 events (8.2%) were reported by the investigators as not resolved by the end of study. It is notable that 9 of the 70 AEs (12.9%; 8 mild and 1 moderate AE) were observed and no treatment was administered; 7 of these events resolved and 2 resolved with sequelae.

Overall, the mean ± SD and median duration of the 70 IOI-related AEs were 77.8 ± 104.9 days and 36.0 days (IQR, 88.0–133 days), respectively. Based on AE severity, the mean ± SD and median duration of the events were: 53.5 ± 68.7 days and 29 days (IQR, 51 days) for mild events, 87.4 ± 95.3 days and 39 days (IQR, 104 days) for moderate events, and 236.8 ± 255.5 days and 133 days (IQR, 279 days) for severe events.

Management of Intraocular Inflammation-Related Adverse Events and Outcomes in Brolucizumab-Treated Eyes. Of the 70 IOI-related AEs, 61 (87.1%) were treated, most with topical corticosteroids (n = 38). Sixteen AEs were treated with a combination of topical corticosteroids and topical antibiotics. Systemic corticosteroids or intraocular corticosteroids were given in combination with topical corticosteroids, topical antibiotics, or both for 3 AEs each (Fig 3). Details of topical, systemic, and intraocular corticosteroids that were administered during the study are presented in Table S3 (available at www.ophthalmologyretina.org). None of the AEs were treated with systemic or intraocular corticosteroids alone. Treatment for IOI-related AEs stratified by IOI severity is presented in Table S4 (available at www.ophthalmologyretina.org).

Among the 61 treated IOI-related AEs, 52 events (85.3%) were reported by the investigators as resolved, 4 events (6.5%) were reported by the investigators as resolved with sequelae, and 5 events (8.2%) were reported by the investigators as not resolved by the end of study. It is notable that 9 of the 70 AEs (12.9%; 8 mild and 1 moderate AE) were observed and no treatment was administered; 7 of these events resolved and 2 resolved with sequelae.

Overall, of the 49 eyes, inflammation resolved in 39 eyes (79.6%), resolved with sequelae in 5 eyes (10.2%), and did not resolve in 5 eyes (10.2%) by the end of study. This was based on a conservative approach in which, in eyes with more than 1 event, the AE with the worst outcome was considered.

In terms of the time to treatment initiation, most of the events were treated within the first 3 days of diagnosis, with most resolving (Table 1). Time to initiation of treatment for IOI-related AEs, classified based on severity, is presented in Table S5 (available at www.ophthalmologyretina.org).

Best-Corrected Visual Acuity Outcomes in Brolucizumab-Treated Eyes. The mean ± SD BCVA change for all 49 eyes with IOI-related AEs from baseline to the end of study was −0.84 ± 20.6 ETDRS letters (Table 2). The VA outcomes of individual eyes with IOI-related AEs at the end of study compared with baseline are presented in Figure 4. Overall, 12
of 49 eyes (24.5%) gained 15 ETDRS letters or more, whereas 9 of 49 eyes (18.4%) lost 15 ETDRS letters or more and 4 of 49 eyes (8.2%) lost 30 ETDRS letters or more. Best-corrected visual acuity outcomes based on maximum severity are presented in Table S6 (available at www.ophthalmologyretina.org).

The mean ± SD BCVA change from before the IOI-related AE to the lowest BCVA in the 3 months after the event was −16.31 ± 17.6 ETDRS letters and from before the IOI-related AE to the end of study was −0.22 ± 18.9 ETDRS letters (Table 2). The proportions of eyes that lost or gained 15 ETDRS letters or more and 30 ETDRS letters or more at these time points are presented in Table 2.

Treatment Continuation with Brolucizumab after First Intraocular Inflammation-Related Adverse Event. A total of 36 of 49 eyes (73.5%) continued brolucizumab treatment after the first IOI-related AE (Table 3). Of these 36 eyes, 24 completed the trial with brolucizumab treatment only, with a mean ± SD BCVA gain of 7.8 ± 13.21 ETDRS letters at the end of study. The remaining 12 eyes discontinued brolucizumab treatment later, because of the occurrence of another AE (n = 8), physician’s decision (n = 1), patient withdrawal (n = 1), lack of efficacy (n = 1), or other undocumented reason (n = 1). Of these 12 eyes, 2 were switched to other anti-VEGF agents during the study.

Thirteen eyes (26.5%) were not treated with another brolucizumab intravitreal injection after the first IOI-related AE; these had a mean ± SD BCVA loss of 10.4 ± 25.52 ETDRS letters (Table 3). Six of these 13 eyes were switched to other anti-VEGF agents and 7 eyes were discontinued from the trial.

Incidence and Description of Retinal Artery Occlusion and Endophthalmitis Adverse Events in Brolucizumab-Treated Eyes

During the HAWK and HARRIER trials, 10 brolucizumab-treated eyes experienced RAO, retinal artery embolism, or retinal artery thrombosis as reported by the investigators; 3 eyes had RAO alone, whereas 7 eyes had both RAO and IOI (Table S7, available at www.ophthalmologyretina.org). Of these 7 eyes, 5 sustained a loss of 15 ETDRS letters or more and 1 achieved a gain of 15 ETDRS letters or more by the end of study (Fig 4). Brolucizumab treatment was withdrawn after the RAO event in 4 of these 7 eyes (Table S7, available at www.ophthalmologyretina.org).

The investigators reported endophthalmitis in 9 brolucizumab-treated eyes, as described in Table S8 (available at www.ophthalmologyretina.org); IOI-related AEs were also reported in 2 of these 9 eyes during the course of the trial. Of these 9 endophthalmitis cases, 2 showed positive culture results, 3 showed negative culture results, and 1 showed interpretable results; in 3 eyes, a culture test was not performed. All of these cases were typically treated with antibiotics, corticosteroids (topical, systemic, and intraocular), or both, with a few eyes requiring additional surgical procedures. By the end of study, 4 of 9 eyes lost 30 ETDRS letters or more, whereas 2 eyes gained 15 ETDRS letters or more from baseline (Table S8, available at www.ophthalmologyretina.org).

Description of Investigator-Reported Intraocular Inflammation-Related Adverse Events in Afibercept-Treated Eyes

Of the 729 eyes treated with afibercept 2 mg in HAWK and HARRIER, 6 eyes (0.82%) experienced 11 investigator-reported IOI-related AEs (5 mild and 6 moderate). Of these 11 AEs, 9 events were reported by the investigators as resolved and 2 events were reported as not resolved by the end of study. Of the 6 eyes, 1 eye gained 15 ETDRS letters or more and 1 eye lost 15 ETDRS letters or more by the end of study.

Case Reports of 2 Brolucizumab-Treated Patients (Eyes) with Investigator-Reported Intraocular Inflammation and Retinal Artery Occlusion

Patient 1: Iridocyclitis Followed by Retinal Artery Thrombosis with a Best-Corrected Visual Acuity Loss of 21 Early Treatment Diabetic Retinopathy Study Letters at the End of Study (from Baseline). A 79-year-old woman randomized to treatment with brolucizumab 6 mg in the left eye showed a baseline BCVA of 70 ETDRS letters. On the second study visit at day 28, BCVA was 59 ETDRS letters and examination showed mild iridocyclitis and a new retinal hemorrhage of 1.5 disc areas in the study eye. She was treated with topical dexamethasone and received a second brolucizumab injection at this visit. After a further 21 days (day 49), she was hospitalized with a diagnosis of severe retinal artery thrombosis in the study eye and showed a BCVA of 63 ETDRS letters (Fig 5A–C). She was treated with intravenous methylprednisolone and oral prednisone. Brolucizumab treatment was discontinued.
permanently after this event and no additional anti-VEGF therapy was given. The iridocyclitis resolved on day 93, and she underwent 3 sessions of panretinal photocoagulation for retinal artery thrombosis (days 129, 132, and 139 of the study), which was ongoing at the time of patient withdrawal from the study on day 471. Her last available BCVA was 49 ETDRS letters (day 156). The investigator assessed the iridocyclitis as not suspected to be related to the study medication or injection procedure and the retinal artery thrombosis as suspected to be related to the study medication but not suspected to be related to the injection procedure.

Patient 2: Uveitis with Retinal Artery Occlusion with a Best-Corrected Visual Acuity Gain of 18 Early Treatment Diabetic Retinopathy Study (ETDRS) Letters at the End of Study (from Baseline). A 69-year-old Asian man randomized to treatment with brolucizumab 6 mg showed a baseline BCVA of 62 ETDRS letters. He sought treatment 11 days after the first brolucizumab injection (day 12) with mild uveitis in the study eye. On day 26, he showed a BCVA of 52 ETDRS letters, and slit-lamp examination showed grade 2 aqueous cells and no aqueous flare. He was treated with topical moxifloxacin, topical betamethasone, topical fluorometholone, and topical bromfenac and continued with the study treatment. The uveitis resolved on day 225. On day 47, 17 days after the second brolucizumab injection, he demonstrated mild RAO in the study eye (Fig 5D, E). He received no treatment for the event but continued brolucizumab study treatment until day 306. He discontinued the study on day 365 because his participation had become “burdensome” owing to a change in personal circumstances, at which point the BCVA was 80 ETDRS letters. Overall during the study, he received treatment with 3 monthly loading doses (weeks 0, 4, and 8) and then treatment every 12 weeks (weeks 20, 32, and 44). On day 653, the RAO event resolved. The investigator assessed RAO as not suspected to be related to the study medication or injection procedure.

Table 3. Proportions of Eyes with at Least 1 Intraocular Inflammation-Related Adverse Event That Were or Were Not Treated with Brolucizumab after the First Event and Their Best-Corrected Visual Acuity Outcomes

| Eyes retreated with brolucizumab after the first IOI-related AE | 36 | 2.6 (17.64) | 7.5 (−5.0 to 15.5) |
| Completed the trial | 32 (88.9) | 3.3 (17.93) | 8.0 (−4.0 to 15.5) |
| Completed the trial and brolucizumab treatment | 24 (66.7) | 7.8 (13.21) | 10.0 (1.0–15.5) |
| Discontinued brolucizumab treatment | 12 (33.3) | −7.7 (21.26) | −4.0 (−21.0 to 7.0) |
| Discontinued the trial | 4 (11.1) | −3.0 (16.15) | −4.5 (−14.0 to 8.0) |
| Eyes not retreated with brolucizumab after the first IOI-related AE | 13 | −10.4 (25.52) | −1.0 (−12.0 to 2.0) |
| Completed the trial | 6 (46.2) | −8.8 (30.43) | 2.0 (−37.0 to 15.0) |
| Discontinued the trial | 7 (53.8) | −11.7 (22.94) | −1.0 (−12.0 to 2.0) |

AE = adverse event; IOI = intraocular inflammation.
related to the study medication or injection procedure and uveitis as suspected to be related to the study medication but not suspected to be related to the injection procedure.

Discussion

After the approval of brolucizumab 6 mg for nAMD, spontaneous reports and published case series have described a spectrum of noninfectious IOI, retinal vasculitis, retinal vascular occlusion, or a combination thereof after intravitreal brolucizumab injection. Although infrequent, these events can be associated with moderate to severe vision loss. Although early clinical data with case reports and series offer preliminary evidence on the incidence and management of these inflammatory events, these are limited by small sample sizes and short follow-up periods. A systematic, multipronged approach is currently underway in an effort to understand better IOI-related AEs after treatment with brolucizumab, in addition to standard safety reporting. Meanwhile, the findings from this post hoc analysis of IOI-related AEs in brolucizumab-treated eyes, as reported during the study by the investigators, provide insights regarding the timing of presentation and management in an effort to understand the outcomes of these events during the study.

In HAWK and HARRIER, more than half of the IOI-related AEs reported with brolucizumab were diagnosed as mild events by the investigators. Most IOI-related AEs (approximately 75%) occurred within 6 months of brolucizumab initiation and after the first 4 injections (approximately 70%). However, some IOI-related AEs were reported as late as 16 months after brolucizumab initiation, after 8 to 10 prior injections, and as late as 72 days after the last brolucizumab injection. Further, nearly one quarter of AEs were noted at unscheduled visits. Therefore, it is important for clinicians to educate patients to promptly report any symptoms of IOI to facilitate timely intervention. Also, it is imperative for clinicians to maintain vigilance and regularly monitor patients receiving brolucizumab for signs of inflammation. A thorough dilated ocular examination should be performed to exclude any signs of IOI before repeating brolucizumab treatment. In view of the current understanding of the spectrum of ocular inflammatory events, widefield imaging techniques should be considered if retinal vasculitis or RAO is suspected. It is also critical to distinguish noninfectious IOI from infectious endophthalmitis because these 2 conditions may have

Figure 5. Images from 2 patients with intraocular inflammation-related adverse events from the HAWK and HARRIER trials. A–C, Patient 1 with iridocyclitis and retinal arterial thrombosis. A, Color fundus photograph demonstrating whitening of the retinal artery consistent with retinal artery occlusion (RAO; white arrowhead) and a cotton-wool spot (black arrowhead). B, Fluorescein angiogram in the venous phase demonstrating nonperfusion of the retinal arteries (white arrowhead) and arterial boxcarring (black arrowhead). C, Spectral-domain OCT image demonstrating cells in the vitreous on the posterior hyaloid. D, E, Color fundus photographs from patient 2 with uveitis and RAO showing small and focal narrowing of retinal arterioles (white arrowheads) and occlusion (black arrowhead).
overlapping clinical presentations but different courses of management.23,24

The management of IOI-related AEs in the HAWK and HARRIER trials typically involved topical corticosteroids, with infrequent use of systemic or intraocular corticosteroids, or both. A small proportion of events resolved without any treatment. The management approaches in HAWK and HARRIER differ from those described in recently published case series where more intensive treatment with systemic or intraocular corticosteroids, or both, has been used in light of the postmarketing reports detailing an inflammatory spectrum of IOI associated with retinal vasculitis, retinal vascular occlusion, or both after brolucizumab treatment.7,17,18,20 Some postmarketing case reports have reported that IOI was the initial presentation and retinal vasculitis or RAO developed on subsequent examination, as well as other reports of improvement of retinal vasculitis and RAO with systemic or intraocular corticosteroids, or both.17,18 In view of these published reports, a recent expert opinion by Baumal et al23 recommends early intensive treatment of IOI, regardless of the severity of the AEs, to minimize the risk of their progression within the spectrum.

In this post hoc analysis, the IOI-related AEs resolved completely in more than three quarters of the eyes (79.6%) and resolved with sequelae in 5 eyes (10.2%) by the end of study. No trends were observed for the recovery outcomes based on the severity of the AE, type or method of treatment given, and time of treatment initiation. Overall, BCVA outcomes from baseline to the end of study were mostly favorable; numerically, more eyes gained than lost 15 ETDRS letters or more by the end of study. Of note, 7 of the 49 eyes with IOI-related AEs also harbored RAO, and most of them showed worse VA outcomes by the end of study. The impact of the IOI-related AEs on visual outcomes was demonstrated by the mean loss of approximately 16 ETDRS letters from before the AE to within 3 months after the AE. However, visual outcomes in these eyes improved over time, and the mean change in BCVA from before the event to the end of study was −0.22 ETDRS letters. This is likely the result of several factors, including management and resolution of AEs and treatment of the underlying nAMD.

After the first IOI-related AE, approximately 74% of eyes received further brolucizumab injections, and most of these eyes (24/36 eyes [approximately 67%]) completed the study with brolucizumab only and achieved an overall BCVA gain by the end of study. It is important to note that, according to the approved label, brolucizumab is contraindicated in eyes with active IOI.5,25 Although the cause of IOI with brolucizumab is not yet known, the delayed onset seems to signal an immune, rather than a toxic or infectious, cause.7,17 However, some study eyes during HAWK and HARRIER were able to continue with brolucizumab therapy after the first IOI event. Further information on the pathogenesis of IOI will support recommendations for repeat brolucizumab injections better. Efforts are ongoing to investigate the root cause of these events. Published case studies propose that inflammation after brolucizumab injection may be caused by local antibodies that may lead to the formation of immune complexes that, through a mechanism of delayed hypersensitivity, may lead to vasculitis.7,17,19 Other proposed causes include prior anti-VEGF treatment use, prior IOI event, human leukocyte antigens, and comorbidities (Ip M, et al. The brolucizumab experience thus far: a health economics and outcomes research analysis. Paper presented at: American Academy of Ophthalmology Virtual Congress; November 2020).7,17–19

Based on the investigator-reported cases, the incidence of IOI-related AEs in aflibercept-treated eyes in HAWK and HARRIER was less than 1%. These AEs were either mild or moderate in severity, with most resolving by the end of study. Of the 6 aflibercept-treated eyes with IOI-related AEs, 1 gained 15 ETDRS letters or more and 1 lost 15 ETDRS letters or more by the end of study. It is important to note that the objective of the current post hoc analysis was to assess the IOI-related AEs in the brolucizumab arm only and not compare that arm with the aflibercept arm.
In a separate post hoc analysis of the HAWK and HARRIER trials, the SRC adopted a discussion-based approach and analyzed investigator-reported cases, including images, of IOI, endophthalmitis, and RAO. They determined whether the AEs were (1) likely to be related to brolucizumab and then (2) reclassified the events within the spectrum of IOI, retinal vasculitis, retinal vascular occlusion, or a combination thereof. Each AE was then designated as definite, probable, or unrelated, regardless of the MedDRA terminology used in the trials. In contrast, the current post hoc analysis evaluated investigator-reported AEs coded to specific preferred terms according to MedDRA version 20.1 that were considered under IOI using a broad and conservative approach to ensure that any potential terms suggestive of IOI were assessed; RAO and endophthalmitis events were not included in this analysis. Furthermore, because codes for retinal occlusive vasculitis were not included in MedDRA version 20.1, no AEs were coded as occlusive vasculitis in HAWK and HARRIER. Based on a more recent understanding of these events, the updated version of MedDRA, expected in October 2021, may allow coding and reporting of occlusive vasculitis.

Despite the differences in the methodology between the 2 post hoc analyses, the findings of the current analysis and that of the SRC may be considered complementary. To understand this further, the 49 eyes with investigator-reported IOI-related AEs were matched against the 50 eyes considered under IOI using a broad and conservative approach to ensure that any potential terms suggestive of IOI were assessed; RAO and endophthalmitis events were not included in this analysis. Furthermore, because codes for retinal occlusive vasculitis were not included in MedDRA version 20.1, no AEs were coded as occlusive vasculitis in HAWK and HARRIER. Based on a more recent understanding of these events, the updated version of MedDRA, expected in October 2021, may allow coding and reporting of occlusive vasculitis.

Footnotes and Disclosures

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The current analysis is based on large phase 3 trials; however, a few limitations apply, including the retrospective post hoc approach. The analysis was conducted in a controlled population of treatment-naïve nAMD patients (according to HAWK and HARRIER eligibility criteria), and no specific management regimens for the AEs were defined in the trial protocols. The findings from this analysis may differ from a clinical setting where both treatment-naïve patients and patients treated previously with other anti-VEGF agents may be given brolucizumab. Finally, because this analysis focused only on investigator-reported IOI-related AEs, infectious endophthalmitis events were excluded from the analysis and RAO events were considered only in relationship to BCVA outcomes.

In summary, findings from this post hoc analysis provide insights to clinicians regarding the timing of presentation, management, and outcomes of IOI-related AEs after brolucizumab treatment. Although most of these events occurred within the first 6 months, delayed presentations of these AEs were also observed. Further, most of the IOI-related AEs either resolved completely or resolved with sequelae by the end of study. Nearly half of eyes with IOI-related AEs lost vision to some degree by the end of study (vs. baseline), and those with the greatest degree of vision loss were eyes that also experienced RAO events. In clinical practice, clinicians should exercise continued vigilance for IOI-related AEs and educate patients to return promptly should symptoms or visual loss develop.

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Abbreviations and Acronyms:
AE = adverse event; ASRS = American Society of Retina Specialists; BCVA = best-corrected visual acuity; EMA = European Medicines Agency; ETDRS = Early Treatment Diabetic Retinopathy Study; IOI = intraocular inflammation; IQR = interquartile range; MedDRA = Medical Dictionary for Regulatory Activities; nAMD = neovascular age-related macular degeneration; PMDA = Pharmaceuticals and Medical Devices Agency; RAO = retinal artery occlusion; ReST = Research and Safety Therapeutics; SD = standard deviation; SRC = safety review committee; VA = visual acuity; VEGF = vascular endothelial growth factor.

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