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Brolucizumab-associated intraocular inflammation in eyes without retinal vasculitis

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Ethical Approval:
This study was deemed exempt from institutional review board oversight based on personal communication with the Human Research Protection Program at Allina Health System (Minneapolis, MN).

Statement of Informed Consent:
As this study did not involve human subjects, but rather deidentified patient information submitted to the ASRS ReST Committee, informed consent was not obtained.

Declaration of Conflicting Interests
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Abstract

Purpose: To analyze a series of eyes with brolucizumab-associated intraocular inflammation (IOI) without retinal vasculitis reported to the American Society of Retina Specialists (ASRS).

Methods: The ASRS Research and Safety in Therapeutics (ReST) Committee analyzed clinical characteristics from submitted reports of IOI after brolucizumab. Eyes with retinal vasculitis or that received intraocular antibiotics were excluded.

Results: Forty-nine eyes of 45 patients were collected. Mean visual acuity (VA) at baseline was 20/49 (range 20/20 – 5/200). Patients presented with IOI a mean of 24 (range 3-63) days after most recent brolucizumab injection; 61% presented for an unscheduled visit while 39% presented at routine follow-up. Mean VA at IOI presentation was 20/67 (range 20/20 – 3/200). Most common symptoms were floaters (78%) and blurry vision (76%). Pain (20%) and redness (16%) were less common; 3 (6%) eyes were asymptomatic. IOI was anterior only in 18%, posterior only in 31%, and both anterior and posterior in 51% of eyes. Treatment included topical steroids alone in 67% eyes, while 10% eyes received no treatment. Mean VA at last follow-up was 20/56 (range 20/20 – 1/200). Three (6%) eyes lost 3 or more lines and 1 (2%) eye lost 6 or more lines.

Conclusions: Brolucizumab-associated IOI without retinal vasculitis typically presented with a delayed onset of a few weeks. Often, visual acuity decline was relatively mild. Most symptoms resolved and nearly all had a return to baseline VA, but a small percentage of patients had a significant decrease in VA at last follow-up.

Introduction:

On October 7, 2019, brolucizumab 6mg (Beovu – Novartis International AG, Basel, Switzerland) was approved by the US Food and Drug Administration (FDA) for treatment of neovascular age-related macular degeneration (NVAMD), with the hope of reducing treatment burden compared to other anti-vascular endothelial growth factor (anti-VEGF) agents. Brolucizumab is a single-chain antibody fragment that blocks all forms of VEGF-A, and can be concentrated to give higher molar equivalent doses than other anti-VEGF drugs due to its highly soluble nature and small molecular weight. The phase 3 HAWK and HARRIER studies demonstrated that brolucizumab had a greater drying effect on the retina than aflibercept.[1] Approximately 50% of patients could be maintained on a q12week brolucizumab dosing regimen with non-inferior visual acuity outcomes compared with q8week aflibercept.[1]

Shortly following the FDA approval of brolucizumab, the American Society of Retina Specialists (ASRS) began receiving reports of inflammation following intravitreal brolucizumab administration for NVAMD. Some of these cases were associated with retinal vasculitis that frequently resulted in vascular occlusion and significant vision loss. Reports of retinal vasculitis associated with intraocular brolucizumab reported to the ASRS have been summarized in a previous report.[2] However, other eyes had intraocular inflammation without retinal vasculitis and were not included in that manuscript. The purpose of this study was to analyze the characteristics of post-approval cases of intraocular inflammation (IOI) without retinal vasculitis voluntarily reported to the ASRS as of June 1, 2020.

Methods:

The ASRS Research and Safety in Therapeutics (ReST) Committee collected and analyzed clinical data from submitted reports of intraocular inflammation without retinal vasculitis that occurred after intravitreal brolucizumab and were reported to the ASRS as of June 1, 2020. Cases with no follow-up data, that were treated with intraocular antibiotics, or that had retinal vasculitis were excluded from the study. Data were tabulated with Microsoft Excel (Microsoft Corporation, Redmond, WA). Snellen visual acuity (VA) was converted to logMAR equivalents for the purpose of analysis. All patient information was deidentified. This study was deemed exempt from institutional review board oversight based on personal communication with the Human Research Protection Program at Allina Health System (Minneapolis, MN).

Initial reports were submitted by treating physicians to the ASRS ReST Committee through the ASRS website (https://www.asrs.org/forms/4/asrs-adverse-event-report-form). The ReST Committee followed up by sending a uniform questionnaire to reporting physicians to collect a standardized data set including location, patient gender, age, eye, race, medical history (including autoimmune disease), allergy history, ocular history, date of neovascular AMD diagnosis, previous number and type of prior anti-VEGF therapy (including most recent therapy preceding brolucizumab), prior history of anti-VEGF-associated inflammation, reason for switching to brolucizumab, number and dates of brolucizumab injection(s), lot number of the causative brolucizumab injection, dates of presentation with an adverse event (AE) and all dates of subsequent follow-up, symptoms at AE presentation, presence or absence and location of intraocular inflammation, grade of intraocular inflammation (anterior chamber and vitreous cells), location of inflammation (anterior, posterior, or both), treatment modalities, final follow-up date, presence or absence of inflammation at final follow-up (and time to resolution if applicable), residual examination findings, residual symptoms, date and type of anti-VEGF re-injection if available (including dates and whether or not there was recurrent inflammation), and anti-VEGF plan moving forward. VA and intraocular pressure (IOP) were recorded from each visit.

Results:

Demographics

In total, there were 39 reporting providers with 62 patients with brolucizumab-associated IOI that were initially reported to the ASRS. In 8 eyes, no follow-up data was provided and they were therefore excluded from analysis. There were another 5 eyes that received intravitreal antibiotics, and were therefore excluded. Another 4 eyes were excluded because of IOI with concurrent retinal vasculitis. In the end, data from 49 eyes of 45 patients with intraocular inflammation without retinal vasculitis after brolucizumab were included in the study; data regarding these cases was submitted by 32 providers. Patient demographics are summarized in Table 1. Twenty-nine (64%) of reported cases occurred in women. Mean age was 76 years, and all were white, consistent with the neovascular AMD population in the US. Reported cases were seen throughout the US. There was no identifiable pattern for previous medical history, ocular history, or drug allergies. Eleven (24%) patients had a

known history of inflammatory or presumed inflammatory disease: 7 with hypothyroidism, 1 with uveitis in the fellow eye, 1 with multiple sclerosis (and hypothyroidism), 1 with Crohn's disease, and 1 with a history of inflammatory liver disease.

Forty-five eyes (92%) had received previous treatment with other anti-VEGF agents, while 4 eyes (8%) were treatment-naïve. Mean number of prior anti-VEGF injections was 26.4 (range 0-62). The most recent anti-VEGF injection prior to brolucizumab was aflibercept in 29 eyes (59%), bevacizumab in 5 eyes (10%), and ranibizumab in 10 eyes (20%). In all eyes, there was a history of 1265 total prior anti-VEGF injections, of which 57% were aflibercept, 27% were ranibizumab, and 15% were bevacizumab. Two eyes had a prior history of aflibercept-associated inflammation. Five patients had same day bilateral injections of brolucizumab, and all 5 had bilateral intraocular inflammation (one of these patients developed a central retinal artery occlusion in one eye, and as that eye was presumed to have retinal vasculitis it was excluded from this analysis).

All adverse events (AEs) arose after 1 (23 eyes, 47%), 2 (20 eyes, 41%) or 3 (6 eyes, 12%) brolucizumab injections in the 8 months since approval (October 7, 2019 to June 1, 2020) and 5 months since a permanent J-code had been established (January 1, 2020). The latest brolucizumab injection reported in this series was on March 27th, 2020. There was no identifiable association with lot number (there were 10 different lot numbers provided from 38 injecting physicians). No brolucizumab injections were given in the presence of concurrent intraocular inflammation as noted by the reporting physician.

Intraocular Inflammation Presentation

Mean time to presentation of IOI was 24 days (median 26, range 3-63 days) from the most recent brolucizumab injection. Mean time between symptom onset and presentation of IOI was 14 days (median 7, range 0 – 53 days). Thirty eyes (61%) presented as an unscheduled visit, while 39% presented with IOI for the first time at routine follow-up visit.

Symptoms at AE onset included floaters (78%), blurry vision (76%), pain (20%), redness (16%), photophobia (4%), and nausea (1%); 3 eyes (6%) were asymptomatic at IOI presentation and throughout follow-up. Mean VA was 20/49 (median 20/40, range 20/20 – 5/200) at baseline (at the time of the causative brolucizumab injection). Mean VA decreased to 20/67 (median 20/50, range 20/25 – 3/200) at AE presentation (see Table 2 for summary of VA data). The location of intraocular inflammation was anterior only in 9 (18%) eyes, posterior only in 15 (31%) eyes, and both anterior and posterior in 25 (51%) eyes. Mean grade of AC cells was 1.1+ cells (range 0.5 - 2+) as graded by the reporting physician, while mean grade of vitreous cells was 1.2+ cells (range 0.5 – 3+) as graded by the reporting physician. Other examination findings at AE presentation included conjunctival injection in 10 (20%) eyes, keratic precipitates in 12 (24%) eyes, and vitreous debris in 21 (41%) eyes. No eyes had corneal edema, anterior chamber fibrin, or hypopyon. Mean IOP was 14.4 mmHg (range 5-21) at the time of most recent brolucizumab injection, and was 15.8 mmHg (6-33) at AE presentation.

Outcomes:

The most recent follow-up visit occurred at a mean of 51 days following AE onset (median 49 days, range 0-128 days), and 74 days following the last brolucizumab (median 76 days, range 5-141 days). At most recent follow-up, mean VA was 20/56 (median 20/40, range 20/20-1/200). Compared to the VA at the time of the causative brolucizumab injection, three (6%) eyes had a >3 line decrease in VA at final follow-up, and one (2%) eye had a >6 line decrease in VA at final follow-up. There were 10 (20%) eyes that had further worsening of VA after IOI presentation. The mean worst VA in the AE course was 20/82 (median 20/60, range 20/25 – 1/200). A sensitivity analysis excluding eyes with less than 30 days follow up since AE presentation revealed similar visual acuity trends (Table 2).

In total, 15 (31%) eyes had residual symptoms at last reported follow-up; symptoms included floaters in 12 (24%) eyes and blurry vision in 6 (12%) eyes. Mean final IOP was 16 mmHg (range 8-28) at most recent follow-up. In terms of inflammation, 32 (65%) eyes had resolution of inflammation over a mean of 26 days (median 14, range 6-80 days). In the subgroup of eyes with greater than 30 days follow-up since AE presentation (32 eyes of 30 patients), 75% had resolution of inflammation at last follow-up visit, and 34% had residual symptoms (floaters and/or blurry vision).

Treatment involved topical corticosteroids alone in thirty-three (67%) eyes while 5 (10%) eyes received no treatment. The remainder were treated with topical and peri- or intra-ocular steroids in 5 (10%) eyes and topical and systemic steroids in 5 (10%) eyes. No eyes had a pars plana vitrectomy and, per exclusion criteria, eyes treated with intravitreal antibiotics were excluded. Of note, one patient expired from a cardiac event deemed unrelated to brolucizumab 8 weeks after the brolucizumab injection associated with IOI.

Anti-VEGF Re-injection:

Thirty-four (69%) of eyes were re-treated with a different anti-VEGF agent after diagnosis of IOI related to brolucizumab. The mean number of re-challenge anti-VEGF injections after IOI presentation was 1.8 (range 1-8 injections) at the time of data collection. Twenty-one (43%) eyes received aflibercept, 8 (16%) eyes received ranibizumab, 2 (4%) eyes received bevacizumab, and 3 (6%) eyes received a repeat brolucizumab injection. Of the 3 eyes that received a brolucizumab re-challenge injection, 2 were in the same patient and both of those eyes received a sub-Tenon’s injection of triamcinolone at the same time as the brolucizumab injection. There were no cases of recurrence or worsening of inflammation after anti-VEGF re-challenge.

Discussion:

As of June 1, 2020 (8 months after FDA approval), the ASRS collected and analyzed data from 49 eyes of 45 patients with intraocular inflammation without retinal vasculitis occurring after intravitreal brolucizumab for neovascular AMD. Most patients (92%) had prior anti-VEGF treatment, while 4 (8%) were treatment naïve. Most patients (61%) came in for an unscheduled visit at the initial IOI presentation, however 39% were only diagnosed with IOI at routine follow-up examination. The most common symptoms were floaters

(78%) and blurry vision (76%); pain was less common (20%). Most eyes had only a mild decrease in VA and regained their baseline VA at last follow up, although 3 eyes (6%) had ≥3-line vision loss and 1 eye (2%) had ≥6-line vision loss at most recent follow-up. At most recent follow-up, most eyes (65%) had resolution of inflammation, and most (69%) had resolution of symptoms. Most eyes (69%) were re-challenged with another anti-VEGF, and there were no reports of recurrent inflammation in those eyes, including the 3 eyes that were re-challenged with brolucizumab.

Intraocular inflammation has been associated with bevacizumab (Genentech, Inc., San Francisco, CA), ranibizumab (Genentech, Inc), and aflibercept (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) at rates between 0.033% – 2.9% per injection.[3] Many cases can be treated successfully with topical or local corticosteroids, although more severe cases are often presumed infectious and treated as such.[3,4] There seems to be an underlying rate of intraocular inflammation with all anti-VEGF drugs, while clusters of higher rates of inflammation may also occur [5-11]. The mechanism of intraocular inflammation after anti-VEGF remains unknown; suggested mechanisms have included immune response to the drug itself, other protein byproducts within the medication, or differences in pH, while mechanisms of inflammation clusters have been attributed to silicone oil residues, silicone/protein aggregates, or endotoxins.[5-11]

In this series, IOI after brolucizumab affected women (64%) more than men, although the disparity was not as great as in our recent series of occlusive retinal vasculitis after brolucizumab (of which 88% of 25 reported patients were in women).[2] This more modest gender disparity, as well as the presenting age and race of patients affected, is consistent with the general neovascular AMD population in the US.[12] There was no identifiable association with any ocular disorders, autoimmune diseases, drug allergies, or other medical disorders.

In phase 3 clinical trials and according to the FDA label, the rate of intraocular inflammation with brolucizumab was higher (>4%) than with its comparator, aflibercept (<1%). The reason for this higher rate of inflammation is currently unknown. The high rates of anti-brolucizumab antibodies noted during HAWK and HARRIER could be an indicator as to the etiology of brolucizumab-associated IOI (and vasculitis). Even before drug initiation, 36-52% of patients had anti-brolucizumab antibodies. After initiation of dosing, anti-brolucizumab antibodies were detected in 53-67% of patients treated with brolucizumab, and by week 88, 23-25% of eyes had induced or boosted levels of anti-brolucizumab antibodies.[13, 14] It was also noted that there was a higher percentage (6%) of patients with intraocular inflammation among patients testing positive for anti-brolucizumab antibodies compared to patients without these antibodies (2%). In comparison to brolucizumab, clinical trials with ranibizumab and aflibercept have shown 0-3% of patients with anti-drug antibodies before treatment initiation and 1-9% of patients with anti-drug antibodies after a 2-year treatment course.[15,16] It is possible that the higher rates of pre-existing and treatment-emergent anti-brolucizumab antibodies may help explain higher rates of inflammation in relation to this drug. Conversely, neither pre-existing nor treatment-emergent anti-brolucizumab antibodies seemed to impact the efficacy of the drug, and the clinical significance of these antibodies remains unclear. Another possibility for the

difference in inflammation rates could be due differences in manufacturing and purification processes. These differences will be important for Novartis and other drug companies to look at when trying to further elucidate the etiology of anti-VEGF-associated IOI.

In the current series, the time course and presentation of inflammation in most eyes suggest a delayed immune reaction to the drug or some component of the delivery system. The delay in presentation and clinical findings is not typical for post-injection endophthalmitis, which most commonly appears within the first week after an injection and is more commonly associated with pain, conjunctival injection, hypopyon, and dense vitritis with a minimal view to the retina.[17] An individual predisposition to brolucizumab-associated IOI may also be suggested by the bilateral onset of IOI in all 5 patients that received bilateral brolucizumab injections (in one of these patients, one eye was excluded from this analysis as that eye also developed retinal vasculitis). Conversely, it is possible that the inflammatory reaction was not related to the drug or the delivery system at all, but rather some part of the injection technique or protocol that was office- or doctor-specific.

One important observation was that 3 eyes in this series had a previous history of aflibercept-associated IOI. If not coincidental, these patients may have either been prone to an inflammatory reaction from anti-VEGF agents in general, or they may have had an immune response to an adjuvant or contaminant present in both drugs (eg. silicone oil residues, silicone/protein aggregates, etc). Conversely, many eyes (69%) were re-challenged with anti-VEGF medications, including 6% with brolucizumab and 43% with aflibercept, and no eyes had recurrence of inflammation, at least on limited follow-up, suggesting that these may be idiosyncratic reactions. The fact that the 3 eyes that were re-challenged with brolucizumab did not have a repeat inflammatory reaction suggests that the reaction may not be to the drug itself, but rather to another component such as a contaminant in the formulation that may vary from vial to vial. If the reaction were an immune reaction to the drug specifically, we would expect a worsening inflammatory response with each injection of the same drug.

Comparison of brolucizumab-associated IOI in this series to anti-VEGF-associated IOI in other published case series should be performed with caution. However, there do appear to be some differences in the presentation and timing of onset of brolucizumab-associated IOI compared to IOI related to other anti-VEGF drugs. In reports of aflibercept-associated IOI, patients presented earlier (around 2-4 days after injection on average), with worse vision, and more commonly with pain (~45%), anterior chamber reaction (75-90%), and corneal edema (13-21%).[7,8] Conversely, in this series of brolucizumab-associated IOI, patients more commonly presented in a more delayed fashion (mean 24 days after injection), and often only presented on routine follow-up (39% of eyes). Compared with aflibercept-associated IOI, patients with brolucizumab-associated IOI (without vasculitis) also had better vision, less commonly with pain (20%), with no reports of corneal edema, with anterior chamber reaction in only 67% of eyes, and more commonly with floaters and vitritis (84%). If these differences are real, the mechanism is unclear. It is also important to note that our series excluded cases of IOI with retinal vasculitis, and may have also excluded more severe cases that were treated with intraocular antibiotics due to suspicion of infectious endophthalmitis.

Without long term follow-up, and with a limited number of cases with a range of severity and treatment approaches, this study was unable to determine optimal treatment modalities. However, 77% of eyes received topical treatment alone or no treatment, and most eyes had recovery of pre-inflammation symptoms, suggesting that topical steroids alone may be sufficient in many cases.

The information in this report is limited to data that was voluntarily submitted to the ASRS ReST Committee by the reporting physicians. Voluntary reporting of safety events is always limited by inevitable under-reporting, and this study was unable to assess incidence of IOI in a real-world setting. Re-review of HAWK/HARRIER data by a Novartis-commissioned Scientific Review Committee identified an IOI rate of 4.6% (including all cases of IOI, both with and without vasculitis) over the course of the two-year trials; IOI without vasculitis in the trial setting occurred at a rate of 1.3% [18]

Follow-up in this study was limited to the termination date of data collection. Similar outcomes results were found when eyes with <30 days of follow up were excluded. However, some patients had ongoing inflammation and loss of vision at last follow-up that may improve with longer follow-up. Similarly, although we identified a small number of patients who had ≥3 and ≥6 line vision loss at last follow up, there were no cases of ≥3 (or ≥6) line vision loss associated with IOI in the absence of vasculitis over 2 years in HAWK/HARRIER.[18]

This study may underestimate the severity of some cases of IOI, as we excluded patients who were treated with intraocular antibiotics to remove potentially confounding cases of infectious endophthalmitis. In addition, this study excluded eyes with retinal vasculitis, a recently-described complication of brolucizumab that is also associated with IOI and also with worse visual outcomes.[2,19]

The information gathered in this study does not indicate a clear etiology of the inflammation. The delayed onset and resolution with topical corticosteroids may suggest an immune reaction to the drug or some component of the drug, but it is unclear what the inciting factor is. Because intraocular cultures and/or PCR testing was not performed, the possibility of indolent infectious causes cannot be ruled out. Future studies of patients with inflammation after intravitreal injections may benefit from the inclusion of this type of testing.

In addition, at the time of this analysis, brolucizumab had been on the market for <8 months. In this series, all cases of brolucizumab-associated IOI arose after 1, 2, or 3 brolucizumab injections, but it is unlikely that patients were treated with many more than 3 injections in that time frame. In HAWK/HARRIER, the Novartis Safety Review Committee identified that 74% of cases of IOI (including with and without vasculitis) occurred within the first 6 months of treatment initiation, with the remainder of cases arising between 6-18 months; no cases arose between 18 and 24 months in this 2-year trial.[18] Longer term real-world experience with this drug will be important to understand if the post-approval experience will be similar to that in the Phase 3 trials.

Although the exact mechanism of these findings remains unclear, the ReST Committee recommends a careful evaluation of the anterior and posterior segment for any signs of active inflammation prior to and after any brolucizumab injection, particularly given the indolent nature of IOI presentation in some eyes. Appropriate informed consent should be obtained, and patients should be advised to return for prompt evaluation with changes. Because all 5 patients that received bilateral same-day brolucizumab injections subsequently developed bilateral IOI, we suggest particular caution when administering this medication (or any newly-approved medication) on the same day bilaterally. Any inflammation following brolucizumab should be followed closely, as occlusive vasculitis has been noted to develop in a delayed fashion in some eyes with IOI. Along the same lines, any consideration of infectious endophthalmitis should be managed accordingly. In the absence of vasculitis or endophthalmitis, most patients with IOI alone in this series appear to return close to their baseline vision with topical steroids, although a small number of eyes in this series did not recover vision. An optimal approach towards re-initiating anti-VEGF therapy is unclear but should ideally be deferred until inflammation has resolved. In this series with limited follow up, recurrent inflammation was not reported when eyes were re-challenged with anti-VEGF. Future analyses of these cases will be important to understand long-term outcomes and management strategies. Analysis of post-marketing data is important with any drug and particularly with newly-approved drugs. The ReST Committee continues to encourage physicians to report any adverse outcomes to the ASRS as well as the drug company.

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Table 1.

Demographic data. NVAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.

Patient number	**49 eyes of 45 patients (one bilateral case)**
Sex	29 Female (64%), 16 Male (36%)
Age	Mean 76 years (Range 56 – 90 years)
Eye	23 right, 23 left, 3 unlisted
Race	All White
Location	All in the United States: 15 Northeast, 9 Western, 14 Southern, 7 Midwest
Autoimmune history 11 (24%) total 4 (13%) excluding hypothyroid	7 hypothyroid 1 Uveitis in fellow eye 1 MS 1 Crohn's disease 1 inflammatory liver disease
Drug allergies	No pattern (49% had no allergies)
Lens	20 phakic (41%) 29 pseudophakic (59%)
Length of NVAMD diagnosis prior to brolucizumab	4 Treatment Naïve (8%) Mean 34 months (Range 0 – 92)
Number of prior anti-VEGF (before brolucizumab)	Mean 26.4 injections (Range 0 - 62) Total 1265 injections
Type of injections prior to brolucizumab (in total)	344 (27%) ranibizumab 195 (15%) bevacizumab 726 (57%) aflibercept
Most recent injection prior to brolucizumab	10 ranibizumab (20%) 5 bevacizumab (10%) 29 aflibercept (59%)
Reason to switch to brolucizumab	Extend treatment interval: 32 eyes (65%) Improve efficacy: 29 eyes (59%) Treatment naive: 4 eyes (8%)

Table 2.

Visual acuity (VA) data. LogMAR = logarithm of the minimum angle of resolution.

ALL EYES (49 eyes of 45 patients)				
	Mean LogMAR VA	**Mean Snellen VA**	**Median Snellen VA**	**Range**
VA at most recent brolucizumab	0.3926	20/49	20/40	20/20 – 5/200
VA at Adverse Event (AE) onset	0.5258	20/67	20/50	20/25 – 3/200
Worst VA	0.6144	20/82	20/60	20/25 – 1/200
VA at most recent follow-up *Mean 74 days since last brolucizumab	0.4457	20/56	20/40	20/20 – 1/200
3 eyes (6%) with ≥ 3-line VA loss at last follow-up, 1 eye (2%) with ≥ 6-line VA loss at last follow-up				
EYES WITH >30 DAYS FOLLOW-UP SINCE AE PRESENTATION (32 eyes of 30 patients)				
VA at most recent brolucizumab	0.4485	20/56	20/40	20/20 – 5/200
VA at AE onset	0.5813	20/76	20/60	20/20 – 5/200
Worst VA	0.6864	20/97	20/75	20/25 – 5/200
VA at most recent follow-up *Mean 92 days since last brolucizumab	0.4739	20/60	20/45	20/20 – 5/200
2 eyes (6%) with ≥ 3-line VA loss at last follow-up, 1 eye (3%) with ≥ 6-line VA loss at last follow-up				