


## REVIEW ARTICLE

# Efficacy and safety of brolucizumab in age-related macular degeneration: A systematic review of real-world studies

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## Abstract

Intravitreally injected anti-vascular endothelial growth factor (anti-VEGF) agents are first-line treatment for neovascular age-related macular degeneration (nAMD). Phase 3 trials demonstrated non-inferiority of anti-VEGF therapy with brolucizumab compared with aflibercept in best corrected visual acuity (BCVA) gains, with superior anatomical outcomes after brolucizumab. The purpose of the review was to summarize real-world efficacy and safety data on brolucizumab in patients with nAMD. The review protocol was registered with PROSPERO (ID: CRD42021290530). We conducted systematic searches in Embase, Medline and key ophthalmology congress websites (19 October 2021). Original reports of efficacy and/or safety in patients receiving brolucizumab to treat nAMD in clinical practice were eligible. The descriptive summary includes reports describing at least 10 brolucizumab-treated eyes. In total, 2907 brolucizumab-treated eyes from 26 studies were included. Outcomes were available for treatment-naïve eyes (six studies), eyes switched to brolucizumab from other anti-VEGFs (16 studies), and/or treatment-naïve and switch eyes combined (eight studies). Follow-up time points ranged from 4 weeks to 1 year post-brolucizumab initiation. For BCVA, significant improvements compared with brolucizumab initiation were reported in four of six studies in treatment-naïve eyes (mean BCVA improvement, range: +3.7 to +11.9 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) and in three of 12 studies in switch eyes (range: +9.0 to +15 ETDRS letters) (all  $p < 0.05$ ); remaining studies reported no significant post-brolucizumab BCVA changes. For central sub-field thickness (CST), improvements post-brolucizumab initiation were reported in all six studies in treatment-naïve eyes (mean CST improvement, range: −113.4 to −150.1  $\mu\text{m}$ ) and in eight of 11 studies in switch eyes (range: −26 to −185.7  $\mu\text{m}$ ) (all  $p < 0.05$ ). The 14 studies reporting on intraretinal, subretinal and/or total fluid observed improvements post-brolucizumab initiation. The four studies comparing treatment intervals observed extension of the interval between injections after switching to brolucizumab from other anti-VEGFs. Incidence of intraocular inflammation ranged from 0% to 19%. In conclusion, real-world efficacy and safety data concur with brolucizumab pivotal trials. Additionally, reduction of disease activity in anti-VEGF switch eyes was demonstrated by fluid reduction and/or visual acuity gain, along with prolongation of the interval between injections.

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## KEYWORDS

brolucizumab, efficacy, neovascular age-related macular degeneration, real-world studies, safety

## 1 | INTRODUCTION

Intravitreal injection (IVI) of an anti-vascular endothelial growth factor (anti-VEGF) agent is the first line of treatment for neovascular (wet) age-related macular degeneration (nAMD), and this has revolutionized patient care in preventing vision loss (Flaxel et al., 2020). Anti-VEGF therapy has efficacy to reduce pathologic exudation, intraretinal fluid (IRF) and/or subretinal fluid (SRF) from macular neovascularization, leading to stabilization or improvement of vision (Flaxel et al., 2020) and enhanced quality of life (Assi et al., 2021). Many studies have shown that frequent injections at intervals as short as every 4 weeks are associated with better visual outcomes (Flaxel et al., 2020; Holz et al., 2020). However, frequent and prolonged IVIs have been associated with patient and caregiver burden (Gohil et al., 2015; McClard et al., 2021).

The pivotal phase 3 HAWK and HARRIER trials on brolucizumab for treatment-naïve patients met their primary endpoint—demonstrating that anti-VEGF therapy with brolucizumab was non-inferior to aflibercept in visual acuity gains, with superior anatomical outcomes regarding retinal fluid compartments and retinal thickness after brolucizumab treatment (Dugel et al., 2020, 2021). In addition, just over 50% of brolucizumab-treated eyes were maintained on a 12-weekly dosing interval through week 48, demonstrating potential for reduced IVI treatment burden with brolucizumab, with comparable efficacy versus the fixed, 8-weekly treatment with aflibercept (Dugel et al., 2020; Tadayoni et al., 2021). Brolucizumab has been associated with infrequent events of intraocular inflammation (IOI), retinal vasculitis and retinal vascular occlusion of 2.1% in patients with nAMD; the overall incidence of at least moderate visual acuity loss associated with IOI was <1% (Khoramnia et al., 2022; Singer et al., 2022). Clinical experience with brolucizumab in nAMD has increased substantially since Food and Drug Administration approval in the USA in October 2019. Patients in real-world scenarios may differ from those in phase 2 and 3 trials, such as in terms of their demographics (e.g., level of comorbidities), disease status (e.g., visual function, retinal fluid presentation) and patterns of care (e.g., treatment-naïve eyes vs. those with prior treatment with other anti-VEGF agents).

The purpose of this systematic review is to summarize the published real-world, post-approval efficacy and safety reports on brolucizumab in treatment-naïve and anti-VEGF switch patients with nAMD, to supplement the phase 3 trial data.

## 2 | METHODS

We submitted the systematic literature review protocol for registration with the International Prospective

Register of Systematic Reviews (PROSPERO) on 10 November 2021, prior to data extraction (PROSPERO registration ID: CRD42021290530). Reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

## 2.1 | Eligibility criteria

All studies describing patients receiving IVI(s) of brolucizumab to treat nAMD in clinical practice were eligible for inclusion in this systematic literature review. All non-interventional studies were eligible, including longitudinal observational studies, case series and individual patient case studies. No language restrictions were implemented.

## 2.2 | Search methods for identifying studies

## 2.2.1 | Data sources

We conducted a systematic literature search in the OVID Embase and OVID Medline databases on 19 October 2021 to identify original reports of efficacy and/or safety in patients with nAMD treated with brolucizumab in clinical practice. In addition, we checked the freely searchable websites of the following key ophthalmology congresses for relevant reports: American Society of Retina Specialists (<https://www.asrs.org/>), Asia-Pacific Vitreo-retina Society (<https://apvrs.org/>), Association for Research in Vision and Ophthalmology (<https://www.arvo.org/>), European Society of Retina Specialists (<https://euretina.org/>), Macula Society (<https://www.maculasociety.org/>) and Retina Society (<https://www.retinasociety.org/>). Eligible congress reports needed to have the abstract or presentation available on the congress website.

## 2.2.2 | Search strategy

The search terms were “brolucizumab”, “Beovu” and “RTH258”. We did not implement any limitations regarding study type at the search stage, and we excluded registration clinical trials at the study selection stage only. The time interval of interest was from 8 October 2019 (the date of the first commercial launch of brolucizumab, which was in the USA) to 19 October 2021 (the date of the systematic literature search). For congress reports identified from the systematic search, we conducted a subsequent targeted search during the report screening and data extraction period (19 October to 30 November 2021) to check for publications of corresponding full papers. We added references from the search results to a reference management program (EndNote X9; Clarivate) and a spreadsheet (Microsoft

Excel) to manage the identified reports and their eligibility status.

## 2.3 | Study selection

Following the systematic literature search, we screened and selected reports based on title, abstract and/or full text. Two reviewers (AB and AM) independently assessed the systematic literature search results and selection of the relevant literature.

## 2.4 | Data collection

Data extraction included publication and study details, patient demographics, anti-VEGF treatment information, and efficacy and safety outcomes. For included congress abstracts, we extracted additional data from the corresponding congress presentations (posters or slides), obtained from the review authors' libraries or from the congress abstract authors. A single researcher extracted the data using a standardized study form. We did not conduct any formal risk of bias assessment.

## 2.5 | Data summary

We summarized the extracted data descriptively. We included studies describing at least 10 brolucizumab-treated eyes in the main descriptive summary, and studies with fewer than 10 brolucizumab-treated eyes in [Tables S1–S4](#). Efficacy outcomes included: change in best corrected visual acuity (BCVA) from baseline before brolucizumab treatment to follow-up time point(s); change in key anatomical parameters from baseline to follow-up time point(s); treatment interval prolongation in comparison to previous anti-VEGF treatment in anti-VEGF-switched eyes; and last recorded treatment interval for treatment-naïve eyes. Summarized safety outcomes included adverse events during follow-up, their treatment and outcomes when available, including ocular adverse events-related visual acuity outcomes. In addition to overall data, whenever available, we presented data for anti-VEGF treatment-naïve eyes separately from treatment-experienced anti-VEGF eyes that were switched to brolucizumab. We converted Snellen or LogMar visual acuity data to Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores for ease of comparison (Ferris et al., 1982).

# 3 | RESULTS

## 3.1 | Search results

We retrieved a total of 407 reports: 235 from Embase, 123 from Medline and 49 from congresses ([Figure 1](#)). Screening by title, abstract and/or full text yielded 49 reports for inclusion, of which 34 were full papers and 15 were congress presentations (five identified via databases and 10 via congresses). We identified a

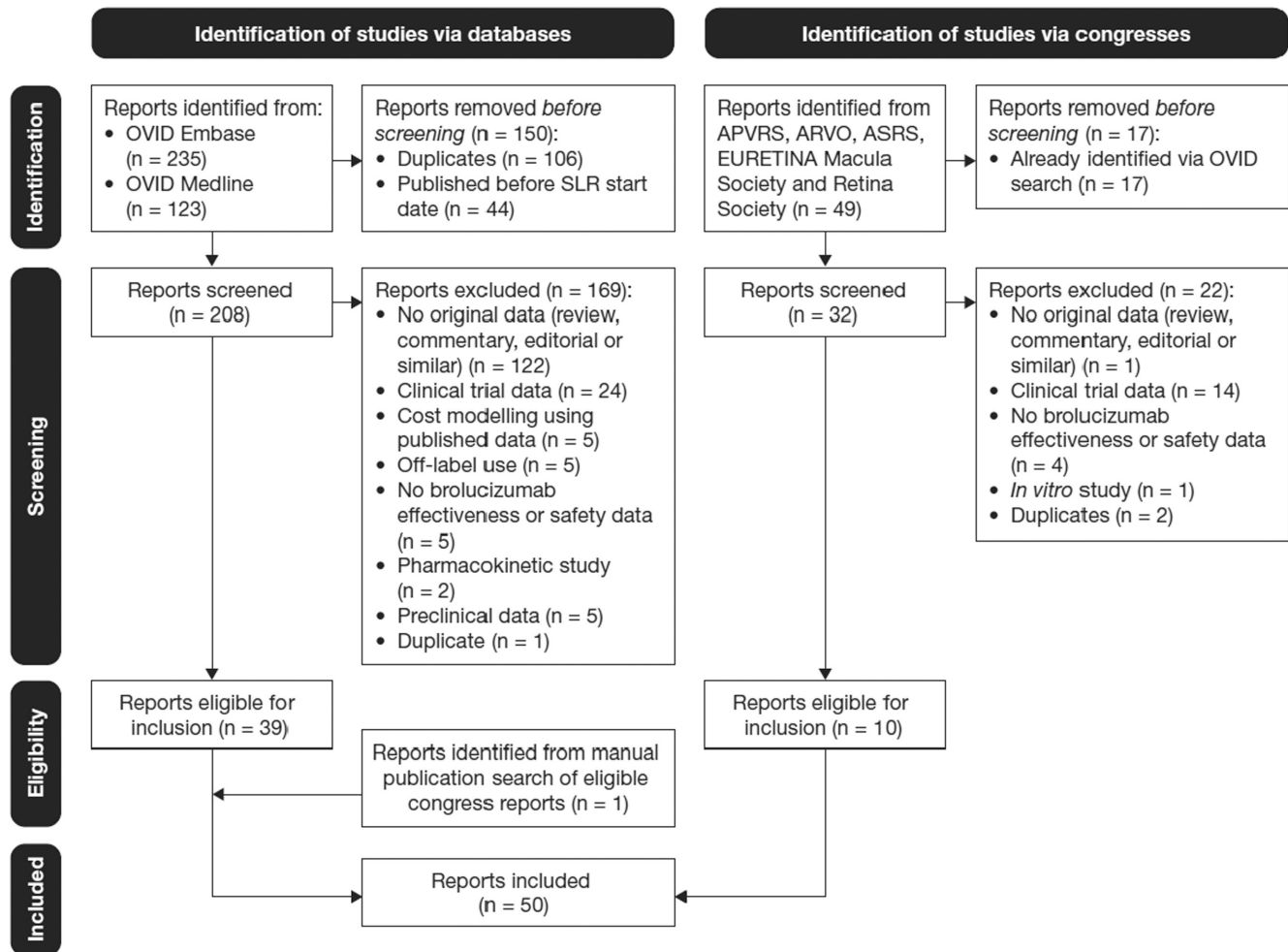
corresponding full paper for one of the included congress presentations by targeted search, bringing the total number of included reports to 50 (comprising 35 full papers and 15 congress presentations). These included reports together described 45 real-world studies of brolucizumab in nAMD. From the reports that were excluded, the most common reasons for exclusion were that no original data were presented ( $n = 123$ ) or that they presented solely clinical trial data ( $n = 38$ ) ([Figure 1](#)).

From the 45 real-world studies (50 reports) for inclusion, 26 studies (31 reports) described at least 10 brolucizumab-treated eyes, and are thus included in the main descriptive summary ([Tables 1–3](#); [Tables S1–S3](#)) (Abdin et al., 2021; Aziz et al., 2021; Baomal et al., 2020; Bilgic, Kodjikian, March de Ribot, et al., 2021; Bilgic, Kodjikian, Srivastava, et al., 2021; Book et al., 2022; Bulirsch et al., 2022; Chakraborty et al., 2021; Cristian et al., 2021; Eandi & Montesl, 2021; Enríquez et al., 2021; Fossataro et al., 2021; Fukuda et al., 2021; Haensli et al., 2021a, 2021b; Hamou et al., 2021; Hussain, 2021; Kilani et al., 2021; Maruko et al., 2021; Matsumoto et al., 2021; Montesl et al., 2021; Rave et al., 2021; Reyes-Capo et al., 2021; Rispoli et al., 2021; Sharma, Kumar, et al., 2021; Sharma, Rave, et al., 2021; Sudhalkar et al., 2021; Walter & Saba, 2021a, 2021b; Witkin et al., 2020, 2021). A further 19 studies (19 reports) describing fewer than 10 brolucizumab-treated eyes are included in [Table S4](#). The majority of these smaller studies (17/19 [89%]) described five or fewer brolucizumab-treated eyes.

## 3.2 | Study characteristics

[Table 1](#) provides an overview of the 26 studies in the main descriptive summary. Further details, including baseline patient demographic and clinical characteristics, are in [Table S1](#). The studies included a total number of 2907 eyes (assuming 40 patients equalled 40 eyes in Cristian et al., 2021).

The studies were conducted in a range of geographical locations: 11 originated in the USA, nine in Europe (Germany: four; Italy: two; Switzerland: two; and UK: one), three in Japan, two in India, and one in Germany and India. Most studies either included only treatment-experienced eyes that were switched to brolucizumab from another anti-VEGF agent (13 studies) or included both switch and treatment-naïve eyes (nine studies). Three studies included only treatment-naïve eyes, and one study did not detail the previous anti-VEGF treatment status of eyes. For outcomes, 16 studies reported data for eyes switched to brolucizumab, eight studies for treatment-naïve and switch eyes combined, and six studies for treatment-naïve eyes. Data on visual acuity outcomes, key anatomical parameters, treatment intervals and safety were reported in 19, 19, 9 and 26 of the studies, respectively. Two of the studies included eyes with polypoidal choroidal vasculopathy (Fukuda et al., 2021; Sudhalkar et al., 2021). None of the included studies reported on patient preferences or patient-reported outcomes.



**FIGURE 1** Flow chart of the systematic literature search. APVRS, Asia-Pacific Vitreo-retina Society; ARVO, Association for Research in Vision and Ophthalmology; ASRS, American Society of Retina Specialists; EURETINA, European Society of Retina Specialists; SLR, systematic literature review.

### 3.3 | Visual acuity

Nineteen studies reported on change in BCVA from brolucizumab initiation to follow-up time point(s) and are included in this section (ocular adverse events-related visual acuity outcomes are captured in the “Safety outcomes” section). The observed change in BCVA at follow-up compared with baseline ranged from −2 to +15 ETDRS letters in the 19 studies that included baseline and follow-up visual acuity data (Table 2 and subsections below). Length of follow-up varied between studies, ranging from 4 weeks to 1 year post-baseline. Overall, data for time points of 3 months, 6 months, and 1 year were reported in four studies, no study, and two studies, respectively.

#### 3.3.1 | Treatment-naïve eyes

Six studies with BCVA data either included only treatment-naïve eyes (three studies) or reported data separately for treatment-naïve eyes (three studies). All six studies included statistical testing for treatment-naïve subgroups. All six studies observed an improvement in BCVA, and in four studies this improvement was significant ( $p < 0.05$ ), ranging from +3.7 ETDRS

letters ( $p = 0.038$ ) in Walter et al. (follow-up not reported) (Walter & Saba, 2021b) to +11.9 ETDRS letters ( $p = 0.011$ ) in Bilgic et al. (mean follow-up 10.4 months) (Bilgic, Kodjikian, Srivastava, et al., 2021). Data for 3 months' follow-up were reported in two of six studies, both of which observed an improvement in mean BCVA (Fukuda et al., 2021; Matsumoto et al., 2021), which was reported as statistically significant in one of the studies (Matsumoto et al., 2021). No studies reported data specifically for the 6-month or 1-year time points for treatment-naïve eyes.

#### 3.3.2 | Anti-VEGF switch eyes

Twelve studies either included only switch eyes (nine studies) or reported data separately for switch eyes (three studies). Ten of the 12 studies included statistical testing for the switch subgroups. Three studies reported significant improvements in mean BCVA in switch eyes, with improvements of +10.4 ETDRS letters ( $p = 0.014$ ) in Bilgic, Kodjikian, March de Ribot, et al. (2021) and +9.0 ETDRS letters ( $p < 0.001$ ) in Chakraborty et al. (2021), although in one study that included several follow-ups, by Abdin et al. (2021), improvements were reported as significant at 16 weeks (+15 ETDRS letters,  $p = 0.03$ ) but



TABLE 1 Overview of studies including at least 10 eyes treated with brolucizumab (26 studies)

Publication	Eyes (patients) (n)	Naive/switch eyes (n)	Mean age (years) <sup>a</sup>	Country (setting)	Switch patients: Previous anti-VEGF agent, mean duration, <sup>a</sup> mean number of injections <sup>a,b</sup>	Reason for anti-VEGF switch to brolucizumab
Abdin et al. (2021)	21 (19)	0/21	76	Germany (single centre)	Number of injections: 39	–
Aziz et al. (2021) (REBEL)	284 (282)	21/263	81.2	USA (multicentre)	–	Persistent fluid: 63.9%; desire to increase treatment interval: 32.3%; match other eye: 1.5%; symptomatic PED: 0.4%; multiple reasons: 1.9%
Baumal et al. (2020)	15 (12)	0/15	77.6	USA (multicentre)	Type: aflibercept, bevacizumab, ranibizumab; number of injections: 27.5	Persistent fluid: 75%; potential for increased durability: 25%
Bilgic, Kodjikian, March de Ribot, et al. (2021) (REBA)	105 (78)	25/80	Naive: 69.2; switch: 74.3	Germany, India (multicentre)	Type: aflibercept, ranibizumab; number of injections: 32.4	Recurrent fluid: 31.3%; recalcitrant fluid: 55.0%; inability to extend: 13.8%
Sudhakar et al. (2021) <sup>c</sup> (REBA PCV)	17 (17)	17/0	–	–	–	–
Bilgic, Kodjikian, Srivastava, et al. (2021) (PROBE)	27 (27)	27/0	65.1	India (multicentre)	–	–
Book et al. (2022) [ePub 2021]	21 (20)	0/21	75.8	Germany (–)	Type: aflibercept, ranibizumab, bevacizumab; duration: 4.3 years; number of injections: 34.3	Persistent fluid: 100%
Bulirsch et al. (2021) (SHIFT)	63 (57)	0/63	79.5	Germany (single centre)	Type: aflibercept, ranibizumab, bevacizumab; duration: 4.2 years; number of injections: 32.5	Recalcitrant fluid: 100%
Chakraborty et al. (2021) (BRAILLE)	94 (94)	20/74	67.6	India (multicentre)	Type: ranibizumab, aflibercept; number of injections: 8.6	Recalcitrant fluid: 100%
Cristian et al. (2021)	– (40)	–	81 <sup>d</sup>	UK (single centre)	Type: aflibercept; number of injections: 16 <sup>d</sup>	Persistent nAMD activity, unstable visual acuity or heavy treatment burden (% NR separately)
Eandi and Montesel (2021), Montesel et al. (2021)	19 (19)	4/15	78.0	Switzerland (single centre)	Type: ranibizumab, aflibercept; number of injections: 25 (ranibizumab), 40 (aflibercept)	Persistent active exudation: 100%
Enriquez et al. (2021)	172 (152)	4/166 <sup>e</sup>	80.0	USA (multicentre)	Type: bevacizumab, ranibizumab, aflibercept; duration: 29.5 months <sup>d</sup> ; number of injections: 18 <sup>d</sup>	Persistent fluid: 65.7%; attempt to extend treatment interval: 30.1%; other/not specified: 4.2%
Fossataro et al. (2021)	11 (11)	0/11	73	Italy (single centre)	Duration: 3 years; number of injections: 12.6	Persistent PED with fluid: 100%
Fukuda et al. (2021)	14 (14)	14/0	74.7	Japan (single centre)	–	–
Haensli et al. (2021a, 2021b)	12 (12)	0/12	80.3 <sup>f</sup>	Switzerland (single centre)	Type: ranibizumab, aflibercept; duration: 4.1 years <sup>f</sup>	Persistent fluid: 100%

(Continues)

TABLE 1 (Continued)

Publication	Eyes (patients) (n)	Naive/switch eyes (n)	Mean age (years) <sup>a</sup>	Country (setting)	Switch patients: Previous anti-VEGF agent, mean duration, <sup>a</sup> mean number of injections <sup>a,b</sup>	Reason for anti-VEGF switch to brolucizumab
Hamou et al. (2021)	99 (88)	10/89	82.0	USA (single centre)	Number of injections: 27.0	–
Hussain (2021)	58 (–)	0/58	82	USA (multicentre)	Type: aflibercept, bevacizumab; number of injections: 26.2	Persistent fluid: 100%
Kilani et al. (2021)	36 (32)	0/36	78.1	Germany (single centre)	Number of injections: 20	Poor response (definition NR): 100%
Maruko et al. (2021)	127 (127)	43/84	–	Japan (multicentre)	–	–
Matsumoto et al. (2021)	42 (40)	42/0	74.9	Japan (single centre)	–	–
Rave et al. (2021), Sharma, Rave, et al. (2021)	144 (144)	0/144	77.6	USA (single centre)	–	–
Reyes-Capo et al. (2021)	766 <sup>g</sup> (–)	–	–	USA (single centre)	–	–
Rispoli et al. (2021)	12 (12)	0/12	78.4	Italy (–)	Type: ranibizumab, aflibercept; number of injections: 13	Persistent fluid: 100%
Sharma, Kumar, et al. (2021) ( <i>BREW</i> )	42 (42)	0/42	79.2	USA (multicentre)	Type: bevacizumab, ranibizumab, aflibercept; number of injections: 19 <sup>d</sup>	–
Walter and Saba (2021a, 2021b)	591 <sup>b</sup> (511 <sup>b</sup> )	61 <sup>b</sup> /530 <sup>b</sup>	80.8	USA (multicentre <sup>h</sup> )	Type: aflibercept, ranibizumab, bevacizumab	–
Witkin et al. (2020)	26 (25)	0/26	79.1	USA (NA <sup>j</sup> )	Type: ranibizumab, bevacizumab, aflibercept; number of injections: 39.1	Extend treatment interval (77%), improve efficacy (73%), worsening vision (4%)
Witkin et al. (2021)	49 (45)	4/45	76	USA (NA <sup>j</sup> )	Type: ranibizumab, bevacizumab, aflibercept; number of injections: 26.4	Extend treatment interval (65%), improve efficacy (59%)

Note: All applicable information was reported when available. Empty cells containing only dashes indicate that the information was not reported or is not applicable.

Abbreviations: NA, not applicable; nAMD, neovascular age-related macular degeneration; NR, not reported; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; VEGF, vascular endothelial growth factor.

<sup>a</sup>Mean unless otherwise indicated.

<sup>b</sup>Number of intravitreal injections with previous anti-VEGF therapy.

<sup>c</sup>The REBA study paper by Bilgic et al. excluded patients with PCV or retinal angiomatous proliferation. The REBA study congress presentation by Sudhalkar et al. included additional data for patients with PCV that were not part of the full paper by Bilgic et al.

<sup>d</sup>Median.

<sup>e</sup>Naive vs. switch not specified for two eyes.

<sup>f</sup>Calculated from data in report.

<sup>g</sup>Eyes with microbial endophthalmitis after anti-VEGF intravitreal injection.

<sup>h</sup>Numbers differ by outcome.

<sup>i</sup>Identified from billing data.

<sup>j</sup>Case reports submitted to the American Society of Retina Specialists (ASRS).

TABLE 2 Visual acuity at baseline and follow-up in studies including at least 10 eyes treated with brolicizumab (19 studies)

Publication (study)	Naive/switch eyes (%)	Eyes (n)	Baseline VA (ETDRS letters) <sup>a</sup>	Follow-up time point(s) <sup>a</sup>	VA at follow-up <sup>a</sup>	Change in VA vs. baseline
Abdin et al. (2021)	0/100	Switch (21)	49	52 weeks <sup>b</sup>	50	+1 <sup>c</sup> ; <i>p</i> = 0.8
Aziz et al. (2021) (REBEL)	7/93	Naive and switch (284)	62.4	44 days	63.4	+1.0 <sup>c</sup> ; <i>p</i> NR
				89 days <sup>d</sup>	64.5	+2.1 <sup>c</sup> ; <i>p</i> NR
Bilgic, Kodjikian, March de Ribot, et al. (2021) (REBA)	24/76	Naive (25)	49.4	10.4 months <sup>e</sup>	61.3 <sup>c</sup>	+11.9; <i>p</i> = 0.011
		Switch (80)	40.0	10.4 months <sup>e</sup>	50.4 <sup>c</sup>	+10.4; <i>p</i> = 0.014
Sudhakar et al. (2021) (REBA PCIV)	100/0	Naive (17)	–	10 months	–	+7.3; <i>p</i> NR
Bilgic, Kodjikian, Srivastava, et al. (2021) (PROBE study)	100/0	Naive (27)	57.4	11.2 months <sup>f</sup>	65.3	+7.8; <i>p</i> = 0.014
Book et al. (2022) [ePub 2021]	0/100	Switch (21)	58.5 <sup>g</sup>	14 weeks	58 <sup>g</sup>	–0.5 <sup>c</sup> ; <i>p</i> = 0.56
Bulirsch et al. (2021) (SHIFT)	0/100	Switch (63)	65.5 <sup>g</sup>	4.3 weeks	64.5 <sup>g</sup>	–1.0 <sup>c</sup> ; <i>p</i> = 0.115
Chakraborty et al. (2021) (BRAILLE)	21/79	Naive and switch (94)	44.5 <sup>g</sup>	7.3 weeks	52 <sup>f</sup>	+7.5 <sup>c</sup> ; <i>p</i> < 0.00001
		Naive (20)	64.5 <sup>g</sup>	– <sub>h</sub>	67 <sup>g</sup>	+2.5 <sup>c</sup> ; <i>p</i> = 0.36
		Switch (74)	39.5 <sup>g</sup>	– <sub>h</sub>	48.5 <sup>g</sup>	+9.0 <sup>c</sup> ; <i>p</i> > 0.00001
Cristian et al. (2021)	0/100	Switch (40)	57 <sup>i</sup>	6 weeks <sup>i</sup>	67.5 <sup>i</sup>	+10.5 <sup>c</sup> ; <i>p</i> NR
Eandi and Montesl (2021), Montesl et al. (2021)	21/79	Naive and switch (19)	65 <sup>g</sup>	14.4 weeks	65 <sup>g</sup>	0 <sup>c</sup> ; <i>p</i> = 0.778
Enrriquez et al. (2021)	2/98	Naive and switch (172)	64.1	59 days <sup>j</sup>	63.3	–0.8; <i>p</i> = 0.65
Fukuda et al. (2021)	100/0	Naive (14)	71.5 <sup>g</sup>	1 month	72.5	+1 <sup>c</sup> ; <i>p</i> = 0.71
				2 months	73	+1.5 <sup>c</sup> ; <i>p</i> = 0.50
				3 months	75	+3.5 <sup>c</sup> ; <i>p</i> = 0.21
Hamou et al. (2021)	10/90	Naive and switch (99)	With IOI (8 eyes): 56	NR (1-year study)	66	+10 <sup>c</sup> ; <i>p</i> NR
			Without IOI (91 eyes): 56	NR (1-year study)	54	–2 <sup>c</sup> ; <i>p</i> NR
Hussain (2021)	0/100	Switch (58)	From aflibercept: 60 <sup>j</sup>	~45 days <sup>k</sup>	60 <sup>j</sup>	0 <sup>c</sup> ; <i>p</i> NS <sup>l</sup>
				~90 days <sup>k</sup>	60 <sup>j</sup>	0 <sup>c</sup> ; <i>p</i> NS <sup>l</sup>
			From bevacizumab: 60 <sup>j</sup>	~45 days <sup>k</sup>	65 <sup>j</sup>	+5 <sup>c</sup> ; <i>p</i> NS <sup>l</sup>
				~90 days <sup>k</sup>	65 <sup>j</sup>	+5 <sup>c</sup> ; <i>p</i> NS <sup>l</sup>
Kilani et al. (2021)	0/100	Switch (36)	52.5 <sup>g</sup>	32 weeks	52.5 <sup>g</sup>	0 <sup>c</sup>
Matsumoto et al. (2021)	100/0	Naive (42)	73 <sup>g</sup>	1 month	76.5 <sup>g</sup>	+3.5 <sup>c</sup> ; <i>p</i> < 0.01
				2 months	78 <sup>g</sup>	+5 <sup>c</sup> ; <i>p</i> < 0.001
				3 months	79 <sup>g</sup>	+6 <sup>c</sup> ; <i>p</i> < 0.001
Rave et al. (2021), Sharma, Rave, et al. (2021)	0/100	Switch (144)	55 <sup>g</sup>	–	–	NS <sup>l</sup>
Rispoli et al. (2021)	0/100	Switch (12)	61 <sup>g</sup>	1 month	62 <sup>g</sup>	+1; <i>p</i> = 0.58
Sharma, Kumar, et al. (2021) (BREW)	0/100	Switch (42)	64 <sup>g</sup>	7.2 weeks	67 <sup>g</sup>	+3 <sup>c</sup> ; <i>d</i> = 0.33

(Continues)

TABLE 2 (Continued)

Publication ( <i>study</i> )	Naive/switch eyes (%)	Eyes ( <i>n</i> )	Baseline VA (ETDRS letters) <sup>a</sup>	Follow-up time point(s) <sup>a</sup>	VA at follow-up <sup>a</sup>	Change in VA vs. baseline
Walter and Saba (2021a, 2021b)	12/88	Naive and switch (59) <sup>m</sup>	60.7	NR (after last IVI)	60.7	−0.1; <i>p</i> = 0.85
		Naive (61) <sup>m</sup>	53.5	NR (after last IVI)	57.2	+3.7; <i>p</i> = 0.038
		Switch (530) <sup>m</sup>	61.6	NR (after last IVI)	61.1	−0.5; <i>p</i> = 0.24

*Note:* All applicable information was reported when available. Empty cells containing only dashes indicate that the information was not reported or is not applicable. Haensli 2021 (Haensli et al., 2021a, 2021b) reports on efficacy outcomes for seven patients only and is thus not included here.

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; IOI, intraocular inflammation; IVI, intravitreal injection; NR, not reported; NS, not statistically significant; PCV, polypoidal choroidal vasculopathy; VA, visual acuity.

<sup>a</sup>Mean unless otherwise indicated.

<sup>b</sup>Study included follow-up at 4, 8, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 weeks. Only the final follow-up is shown here.

<sup>c</sup>Calculated from data reported in the study.

<sup>d</sup>This follow-up time was calculated by adding the mean days between the first and second injections and the second and third injections. However, because *n* numbers decreased this value is an approximation only.

<sup>e</sup>Patients had to be followed up for at least 9 months to be included in the study.

<sup>f</sup>Patients had to be followed up for at least 10 months to be included in the study.

<sup>g</sup>Converted from LogMar (Ferris et al., 1982).

<sup>h</sup>Follow-up was 7.3 weeks overall; not reported separately for naive and switch groups.

<sup>i</sup>Median.

<sup>j</sup>Converted from Snellen at 20 feet (Ferris et al., 1982).

<sup>k</sup>Values read off graph.

<sup>l</sup>Actual values not reported.

<sup>m</sup>*n* numbers differ by outcome.



TABLE 3 Safety outcomes in studies including at least 10 eyes treated with brolocizumab (26 studies)

Publication (study)	Naive/switch eyes (%)	Eyes (n)	Follow-up <sup>a</sup>	Systemic adverse events	Ocular adverse events, n (%) of eyes	Timing	Treatment (outcome)
Abdin et al. (2021)	0/100	21	1 year	–	Iritis: 1 (4.8%) Vitreitis: 1 (4.8%) Ocular hypertension: 1 (4.8%) Cerebral vascular accident: 1 (4.8%)	Week 24 Week 12 Week 16 Week 32	– – – –
Aziz et al. (2021) (REBEL)	7/93	Naive and switch (284)	89 days <sup>b</sup>	–	Pain: 3 (1.1%) Uveitis: 10 (3.7%)	– –	Iritis, 1 case: prednisolone (outcome: resolved); IOI, 9 cases: prednisolone (outcome: all resolved) Prednisolone (outcome: unresolved)
Baumal et al. (2020)	0/100	Switch (15)	NR (1–3 brolocizumab IVIs)	–	Retinal vasculitis: 15 (100.0%) [study inclusion criterion]; 7 (47%) with occlusion of larger retinal arteries at optic nerve or branches proximal to fovea	Mean 30 days (range 7–56 days) after brolocizumab IVI	Systemic, intravitreal, and/or topical corticosteroids (outcome: mean VA reduced vs. baseline); 2 eyes underwent vitrectomy (outcome: no improvement in VA)
Bilgic, Kodjikian, March de Ribot, et al. (2021) (REBA)	24/76	Naive and switch (105)	10.4 months	–	Macular hole: 1 (1.0% overall, 1.3% of switch group eyes)	15 days after 5th brolocizumab IVI	Macular hole surgery (outcome: VA improved/recovered and stabilized)
Bilgic, Kodjikian, Srivastava, et al. (2021) (PROBE)	100/0	Naive (27)	11.2 months	–	Branch arterial occlusion: 1 (1.0% overall, 1.3% of switch group eyes) IOI: 0 (0%) Post-injection endophthalmitis or vision loss: 0 (0%)	7 days after 5th brolocizumab IVI –	Low molecular weight heparin (outcome: complete recovery) –
Book et al. (2022) [Epub 2021]	0/100	Switch (21)	NR (~18–20 weeks)	–	IOI with uveitis: 2 (9.5%)	1 patient after 1st brolocizumab injection; 1 patient after end of loading phase	Corticosteroid eyedrops (outcome: no complications)
Bulirsch et al. (2021) (SHIFT)	0/100	Switch (63)	16 weeks	–	Vitreous haemorrhage (considered procedure-related): 1 (1.6%) IOI: 7 (11.1%) overall (2 with anterior uveitis, 4 with intermediate uveitis, 1 [1.6%] with segmental periartertolar sheathing)	– 4 patients after 1st brolocizumab injection; 3 patients after 2nd brolocizumab injection	No treatment (outcome: resolved spontaneously) Topical corticosteroid for mild cases, supplemented with subconjunctival/systemic corticosteroid for moderate/severe cases (outcome: no persistent clinically relevant VA changes once IOI had ceased)

(Continues)

TABLE 3 (Continued)

Publication (study)	Naive/switch eyes (%)	Eyes (n)	Follow-up <sup>a</sup>	Systemic adverse events	Ocular adverse events, n (%) of eyes	Timing	Treatment (outcome)
Chakraborty et al. (2021) (BRAILLE)	21/79	Naive and switch (94)	7.3 weeks	Serious: 0 (0%)	Subretinal haemorrhage (SAE): 2 (1.6%) <sup>c</sup> Retinal pigment epithelial tear (SAE): 1 (0.8%) <sup>c</sup> Mild ocular pain: 18 (14.3%) <sup>c</sup> Burning sensation: 6 (4.5%) <sup>c</sup> Subconjunctival haemorrhage: 4 (3.2%) <sup>c</sup>	–	–
Cristian et al. (2021)	0/100	Switch (40)	6 weeks <sup>d</sup>	–	Retinal vasculitis with vascular occlusion: 1 (2.5%)	–	–
Eandi and Montesel (2021), Montesel et al. (2021)	21/79	Naive and switch (19)	14.4 weeks	–	IOI: 1 (5.3%)	3 days after 2nd brolucizumab injection	Corticosteroid eyedrops and oral (outcome: resolved)
Enríquez et al. (2021)	2/98	Naive and switch (172)	59 days <sup>d</sup>	Headache: 1 (0.6%) Cerebrovascular accident: 1 (0.6%)	IOI without retinal artery occlusion: 13 (7.6%) <sup>e</sup>	9 patients after 1st, 3 patients after 2nd and 2 patients after 3rd brolucizumab injection (median 49 days from injection)	6 cases: no treatment (outcome: spontaneous resolution); 1 case: topical corticosteroid (outcome: corticosteroid resolution); 6 cases: topical and/or oral corticosteroid, 1 with subTenon's (outcome: NR)
					IOI with retinal artery occlusion: 1 (0.6%) <sup>f</sup>		Vitrectomy and intraoperative triamcinolone (outcome: NR)
					Endophthalmitis: 1 (0.6%)	–	Intravitreal antibiotic treatment (outcome: adequate response)
					Vitreous opacity without IOI: 1 (0.6%) Intraocular pressure elevation: 1 (0.6%) Posterior vitreous detachment: 1 (0.6%)	–	–
					Side effects: 0%	–	–
Fossataro et al. (2021)	0/100	Switch (11)	2 months	–	IOI without retinal artery occlusion: 1 (7.1%)	After 2nd brolucizumab injection	Topical corticosteroid (outcome: resolution)
Fukuda et al. (2021)	100/0	Naive (14)	3 months	–	IOI with retinal artery occlusion: 1 (7.1%)	After 3rd brolucizumab injection	No appropriate prompt treatment (outcome: visual field loss remained)
					IOI with extra-macular vascular occlusion: 2 (16.7%)	1 patient after 1st brolucizumab injection; 1 patient after 2nd brolucizumab injection	Systemic steroid treatment (outcome: recovery)
Haensli et al. (2021a, 2021b)	0/100	Switch (12)	1 year	Transient ischaemic attack: 1 (8.3%) (outcome: recovery)	Ocular ischaemic syndrome: 1 (8.3%) <sup>g</sup>	After >6 months from 1st brolucizumab injection <sup>g</sup>	(outcome: visual loss)

TABLE 3 (Continued)

Publication (study)	Naive/switch eyes (%)	Eyes (n)	Follow-up <sup>a</sup>	Systemic adverse events	Ocular adverse events, n (%) of eyes	Timing	Treatment (outcome)
Hamou et al. (2021)	10/90	Naive and switch (99)	1 year	–	IOI without retinal vasculitis: 6 (6.1%) IOI with retinal vasculitis: 2 (2.0%)	Average 1.6 brolocizumab injections to start of IOI; 81 days from 1st brolocizumab injection	–
Hussain (2021)	0/100	Switch (58)	~3.0–4.5 months <sup>b</sup>	–	Retinal vasculitis, vascular occlusion or vitritis: 0 (0%)	–	–
Kilani et al. (2021)	0/100	Switch (36)	32 weeks	–	Retinal occlusive vasculitis with vitritis: 1 (2.8%) Uveitis: 4 (11.1%)	4 of 5 IOIs between 3rd and 4th brolocizumab injection (8–16 weeks after 1st injection)	Immediate systemic topical steroid therapy (outcome: visual impairment not permanent)
Maruko et al. (2021)	34/66	Naive and switch (127)	12.4 weeks	–	IOI without retinal vasculitis/vascular occlusion: 8 (6.3%) IOI with retinal vasculitis: 2 (1.6%)	9 eyes after 1st brolocizumab injection (mean 23 days after injection); 3 eyes after 2nd or 3rd injection	Topical corticosteroids (outcome: resolution) Topical corticosteroids and subTenon's triamcinolone acetamide (outcome: resolution)
Matsumoto et al. (2021)	100/0	Naive (42)	3 months	Cerebral infarction: 0 (0%) Myocardial infarction: 0 (0%)	IOI with retinal vasculitis and with retinal vascular occlusion: 2 (1.6%)	–	Topical corticosteroids and subTenon's triamcinolone acetamide (outcome: visual acuity decrease improved in 1 month) SubTenon's triamcinolone acetamide and betamethasone eye drops (outcome: ameliorated)
Rave et al. (2021), Sharma, Rave, et al. (2021)	0/100	Switch (144)	–	–	IOI: 16 (11.1%), of which 7 with uveitis, 4 with retinal artery occlusion and 6 with anterior chamber inflammation	–	–
Reyes-Capo et al. (2021)	–	NR (766)	–	–	Microbial endophthalmitis: 0 (0%) Other safety outcomes NR	–	–
Rispoli et al. (2021)	0/100	Switch (12)	1 month	0 (0%)	0 (0%)	–	–
Sharma, Kumar, et al. (2021) (BREW)	0/100	Switch (42)	7.2 weeks	0 (0%)	IOI, vasculitis or other ocular adverse effects: 0 (0%)	–	–
Walter and Saba (2021a, 2021b)	12/88	Naive and switch (626) <sup>c</sup>	– <sup>d</sup>	–	IOI: 29 (4.6%), of which 3 with retinal vasculitis and 1 with retinal vascular occlusion Urticarial rash: 1 (0.2%)	After an average of 2 brolocizumab injections	–

TABLE 3 (Continued)

Publication (study)	Naïve/switch eyes (%)	Eyes (n)	Follow-up <sup>a</sup>	Systemic adverse events	Ocular adverse events, n (%) of eyes	Timing	Treatment (outcome)
Witkin et al. (2020)	0/100	Switch (26) <sup>k</sup> (49) <sup>k</sup>	NR (1–3 brolicizumab IVIs)	–	Retinal vasculitis: 26 (100.0%) [study inclusion criterion] <sup>k</sup> , of which 83–88% with retinal vascular occlusion and/or retinal ischaemia	11 eyes after 1st, 11 eyes after 2nd and 4 eyes after 3rd brolicizumab injection (mean 26 days from most recent injection to presentation)	Topical, systemic and/or intravitreal corticosteroids (92.3%); pars plana vitrectomy (15.4%); no treatment (7.7%) (outcome: mean VA was 20/243 at last follow-up, compared with 20/52 before the adverse event and 20/151 at presentation of the adverse event)
Witkin et al. (2021)	8/92	Naïve and switch (49) <sup>k</sup>	NR (1–3 brolicizumab IVIs)	–	IOI without retinal vasculitis: 49 (100.0%) [study inclusion criterion] <sup>k</sup>	23 eyes after 1st, 20 eyes after 2nd and 6 eyes after 3rd brolicizumab injection (mean 24 days from most recent injection to presentation)	Topical, periocular, intraocular and/or systemic steroids (outcome: at last follow-up: “most” [actual value NR] regained baseline VA)

Note: All applicable information was reported when available. Empty cells containing only dashes indicate that the information was not reported or is not applicable.

Abbreviations: IOI, intraocular inflammation; IVI, intravitreal injection; NR, not reported; SAE, serious adverse event; VA, visual acuity.

<sup>a</sup>Mean unless otherwise indicated.

<sup>b</sup>This follow-up time was calculated by adding the mean days between the first and second injections and the second and third injections. However, because n numbers decreased this value is an approximation only.

<sup>c</sup>Percentage values are for number of events per total number of injections.

<sup>d</sup>Median.

<sup>e</sup>An additional case with IOI was considered of uncertain association with brolicizumab.

<sup>f</sup>The eye with IOI and occlusive retinal vasculitis was also reported in the series from Bauman et al. (2020).

<sup>g</sup>Timing NR. This adverse event is noted in the congress presentation with 12-month follow-up but not the full paper with 6-month follow-up, suggesting that it occurred after 6 months. The eye dropped off the study before the end of the 6-month follow-up, and the authors noted the event as “possibly related” to brolicizumab.

<sup>h</sup>Values read off graph.

<sup>i</sup>n number is for safety outcomes; n numbers differ by outcome.

<sup>j</sup>Mean/median follow-up not reported. Patients who developed adverse events had received an average of two intravitreal injections of brolicizumab.

<sup>k</sup>Case reports submitted to the American Society of Retinal Specialists.

not at earlier or later time points. Seven studies observed no statistically significant changes in mean BCVA in switch eyes. The two studies that did not report on statistical significance either observed no numerical change or found a numerical improvement in BCVA in switch eyes. Data specifically for the 3-month and 1-year follow-up time points were reported in one study each, neither of which observed statistically significant changes. No studies specifically reported data for the 6-month time point for switch eyes. We observed no obvious association patterns between visual acuity outcomes and previous treatment (agent, duration or number of injections) or reason for switch.

### 3.3.3 | Treatment-naïve and anti-VEGF switch eyes

Four studies included both treatment-naïve and switch eyes and did not report data separately for the two groups. Two studies included statistical testing and observed no statistically significant changes in mean BCVA across treatment-naïve and switch eyes combined. Data for 3-month and 1-year follow-up were provided in one study each, neither of which reported on statistical significance. None of the studies reported 6-month data.

## 3.4 | Anatomical parameters

In the 19 studies that included baseline and follow-up data on key anatomical parameters, the reported follow-up time points ranged from 1 month to 1 year post-baseline (Table S2). Overall, data for time points of 3 months, 6 months, and 1 year were reported in four studies, no study, and 1 study, respectively. Data on central subfield thickness (CST) at baseline and follow-up were reported in 17 studies.

### 3.4.1 | CST, treatment-naïve eyes

Six studies either included only treatment-naïve eyes (three studies) or reported data separately for treatment-naïve eyes (three studies). All of these six studies reported a significant reduction in mean CST from brolocizumab initiation to follow-up in treatment-naïve eyes, ranging from  $-113.4 \mu\text{m}$  ( $p < 0.001$ ) (mean follow-up 7.3 weeks) (Chakraborty et al., 2021) to  $-150.1 \mu\text{m}$  ( $p = 0.021$ ) (mean follow-up 10.4 months) (Bilgic, Kodjikian, March de Ribot, et al., 2021). Data for 3-month follow-up were reported in two of the six studies, both of which reported statistically significant improvements in CST. No studies reported 6-month or 1-year CST data for treatment-naïve eyes.

### 3.4.2 | CST, anti-VEGF switch eyes

Eleven studies reporting on CST either included only switch eyes (eight studies) or reported data separately for switch eyes (three studies). Nine of the 11 studies

included statistical testing for the switch subgroups, of which eight studies observed a significant improvement in mean CST in switch eyes, ranging from  $-26 \mu\text{m}$  (actual  $p$  value not reported) (mean follow-up about 3 months) (Hussain, 2021) to  $-185.7 \mu\text{m}$  ( $p = 0.01$ ) (mean follow-up 10.4 months) (Bilgic, Kodjikian, March de Ribot, et al., 2021). Data for 3-month and 1-year follow-up were reported in one study each, both of which observed statistically significant improvements in CST. No studies reported 6-month CST data for switch eyes.

### 3.4.3 | CST, treatment-naïve and anti-VEGF switch eyes

Three studies included treatment-naïve and switch eyes and did not report data separately for the two groups. Two studies included statistical testing, and both observed a significant improvement in mean CST across treatment-naïve and switch eyes combined. Data for 3-month follow-up were reported in one study, which did not report on statistical significance. No studies reported 6-month or 1-year CST data.

### 3.4.4 | Fluid status

Data on the presence of total fluid, IRF and/or SRF at baseline and follow-up were reported in 14 studies. Of these, two studies reported data for treatment-naïve eyes, seven for switch eyes, and five for treatment-naïve and switch eyes combined.

Ten studies reported on presence of IRF, of which five reported data for switch eyes, and five reported data for treatment-naïve and switch eyes combined. All 10 studies observed an improvement (i.e., reduction in the proportion of eyes with IRF present) at follow-up compared with baseline. In one of the two studies that reported on statistical testing, the improvement was significant.

Twelve studies reported on presence of SRF, of which one reported data for treatment-naïve eyes, six for switch eyes, and five for treatment-naïve and switch eyes combined. All 12 studies reported a reduction in the proportion of eyes with SRF present at follow-up compared with baseline. In three studies that reported on statistical testing, the improvement was significant.

Two studies reported on presence of fluid overall at baseline and follow-up, both of which observed an improvement (statistical significance not reported). Two studies reported on macular volume at baseline and follow-up; significant improvements were observed in both treatment-naïve and switch eyes (Bulirsch et al., 2022; Walter & Saba, 2021a, 2021b).

## 3.5 | Intervals between brolocizumab treatments

Four studies compared treatment intervals with previous anti-VEGF treatment and treatment intervals after switching to brolocizumab. All four studies observed extension of the treatment interval (Table S3). Two studies



tested for significance and observed significant interval increases.

Rave et al. assessed treatment intervals for 144 switch eyes (144 patients) on a treat-and-extend regimen (follow-up time not reported) (Rave et al., 2021; Sharma, Rave, et al., 2021). The average treatment interval was extended from 34 days pre-switch to 60 days post-switch to brolucizumab ( $p < 0.001$ ) (Rave et al., 2021; Sharma, Rave, et al., 2021).

Walter et al. evaluated 591 treatment-naïve and anti-VEGF switch eyes (511 patients; follow-up time not reported) (Walter & Saba, 2021a, 2021b). Mean treatment interval was 6.3 weeks pre-switch and 6.8 weeks post-switch ( $p = 0.001$ ) (Walter & Saba, 2021a, 2021b). These authors also assessed the brolucizumab treatment interval separately by previous anti-VEGF treatment interval (Walter & Saba, 2021a, 2021b). Significant increases in interval means were observed in subgroups with previous treatment intervals up to 6 weeks (Walter & Saba, 2021a). In the subgroup that had a treatment interval of more than 8 weeks with previous anti-VEGF treatment, a significant decrease in interval mean was observed with brolucizumab (Walter & Saba, 2021a). There was no significant change in mean interval length for the group with a previous 6–8-week interval (Walter & Saba, 2021a).

In the REBA study, which included 105 eyes of 78 patients, the proportion of patients with a 12-weekly brolucizumab treatment interval was 64.0% in the treatment-naïve group and 31.3% in the switch group at the end of follow-up (mean 10.4 months). The remaining patients had an 8-weekly treatment interval (Bilgic, Kodjikian, March de Ribot, et al., 2021). The study did not report the pre-switch interval with previous anti-VEGF treatment (Bilgic, Kodjikian, March de Ribot, et al., 2021).

Cristian et al. (2021) reported a 3-week increase in maximal median injection interval with brolucizumab, from a maximal median of 6 weeks with previous treatment, in a study of 40 switch eyes.

### 3.6 | Safety outcomes

From the 26 studies that included variable details of adverse events, the reported follow-up ranged from 1 month to 1 year. Table 3 provides a comprehensive listing of the safety events as presented in each of the original studies. Information was limited as to how events were defined and how patients were monitored during follow-up. Six studies reported no adverse events occurring during follow-up (Bilgic, Kodjikian, Srivastava, et al., 2021; Fossataro et al., 2021; Hussain, 2021; Reyes-Capo et al., 2021; Rispoli et al., 2021; Sharma, Kumar, et al., 2021). For three studies, ocular adverse events were an inclusion criterion (Baumal et al., 2020; Witkin et al., 2020, 2021).

Twenty studies reported on IOI. Two studies reported no events of IOI (Bilgic, Kodjikian, Srivastava, et al., 2021; Sharma, Kumar, et al., 2021); the PROBE study of 27 treatment-naïve eyes (mean 11-month follow-up) (Bilgic, Kodjikian, Srivastava, et al., 2021) and

the BREW study of 42 switch eyes (mean 7-week follow-up) (Sharma, Kumar, et al., 2021). The highest incidence of IOI was 19.0% in a study from Japan, which included 42 treatment-naïve eyes receiving three monthly loading injections; amelioration was shown in response to steroid therapy (combination of subTenon's triamcinolone acetonide injection and betamethasone eye drops), none of the eyes lost BCVA, and a statistically significant vision improvement was observed at 3 months for eyes receiving their first three monthly injections (Matsumoto et al., 2021). Three US studies had IOI and/or retinal vasculitis as study inclusion requirements (Baumal et al., 2020; Witkin et al., 2020, 2021); Baumal et al. (2020) included 15 switch eyes, Witkin et al. (2020) included 26 switch eyes, and Witkin et al. (2021) included 49 treatment-naïve and switch eyes.

Sixteen studies reported on occlusive vasculitis events. Two US studies reported no events (Hussain, 2021; Sharma, Kumar, et al., 2021); Hussain et al. studied 58 anti-VEGF switch eyes (follow-up approximately 3.0–4.5 months; mean follow-up not reported) (Hussain, 2021) and Sharma et al. (BREW) included 42 switch eyes (mean follow-up 7 weeks) (Sharma, Kumar, et al., 2021); there were no reported cases of retinal vasculitis, vascular occlusion or vitritis (Hussain, 2021; Sharma, Kumar, et al., 2021). The highest incidence was 16.7% in a study from Switzerland, by Haensli et al. (2021a, 2021b), that included 12 switch eyes with a 1-year follow-up, with no associated vision loss; one eye that dropped off the study had ocular ischaemic syndrome with visual loss. Two US studies had retinal vasculitis as a study inclusion criterion (Baumal et al., 2020; Witkin et al., 2020); 47% of the 15 switch eyes included in Baumal et al. had occlusion of larger retinal arteries at the optic nerve or branches proximal to the fovea (Baumal et al., 2020), and 83–88% of the 26 switch eyes included in Witkin et al. had retinal vascular occlusion and/or retinal ischaemia (Witkin et al., 2020). Mean visual acuity in Baumal et al. was 63.7 ETDRS letters before switching to brolucizumab, 36.0 ETDRS letters at diagnosis of retinal vasculitis ( $p = 0.008$ ) and 43.4 ETDRS letters after a mean follow-up of 25 days, which was reduced compared with baseline ( $p = 0.033$ ) (Baumal et al., 2020).

A separate systematic review is in preparation of adverse events following brolucizumab use in the real world.

## 4 | DISCUSSION

This systematic literature review of the efficacy and safety of brolucizumab in clinical practice summarizes the published data in eyes with nAMD in the real-world setting. Mean visual acuity gains with brolucizumab that were statistically significant were reported in four of six anti-VEGF treatment-naïve studies (range: +3.7 to +11.9 ETDRS letters;  $p < 0.05$ ) and in three of 12 anti-VEGF switch studies (range: +9.0 to +15 ETDRS letters;  $p < 0.05$ ); the remaining studies observed no significant BCVA changes. Improvements in anatomical outcomes seen in phase 3 randomized controlled trials (Dugel et al., 2020, 2021; Khanani et al., 2022) were confirmed in

real life, with statistically significant CST improvements in all six studies in treatment-naïve nAMD eyes (range:  $-113.4$  to  $-150.1$   $\mu\text{m}$ ;  $p < 0.05$ ) and in eight of 11 studies in switch nAMD eyes (range:  $-26$  to  $-185.7$   $\mu\text{m}$ ;  $p < 0.05$ ). Reductions in IRF and SRF were observed in all studies reporting on these parameters (10 and 12 studies, respectively), but few tested the statistical significance. We did not determine overall means or medians across studies because of heterogeneity between studies in terms of confounders such as treatment duration, which have an impact on the respective outcomes.

Anti-VEGF therapy is commonly initiated in treatment-naïve eyes using three loading doses at 4-week intervals, with subsequent follow-up and treatment intervals depending on clinical findings (mainly anatomical outcomes; Kodjikian et al., 2021), physician judgement and type of anti-VEGF therapy used (Flaxel et al., 2020). Interval extension was seen in the pivotal trials and was also observed in real life; interval extensions were reported for patients switched from previous anti-VEGF therapy to brolucizumab, and a 12-week brolucizumab treatment interval was possible in 64% of patients who were treatment naïve (Bilgic, Kodjikian, March de Ribot, et al., 2021). However, follow-up times were short. In the study by Walter et al. that included 511 patients, follow-up time was not reported but is likely to have included only the first 7.5 months of brolucizumab use in the USA, in a setting in which brolucizumab was newly launched and physicians may have been cautious about interval extensions (Walter & Saba, 2021a, 2021b).

Reporting of safety events was heterogeneous and inconsistent between studies. Follow-up time ranged from 1 month to 1 year. Incidence of IOI ranged from 0% in two studies that included 27 treatment-naïve eyes (mean 11-month follow-up) and 42 switch eyes (mean 7-week follow-up), respectively (Bilgic, Kodjikian, Srivastava, et al., 2021; Sharma, Kumar, et al., 2021), to 19% in a study of treatment-naïve eyes (Matsumoto et al., 2021); BCVA did not deteriorate as a result in any of these eyes. Limited impact on visual acuity is possibly due to the anatomical location of the retinal vasculitis in the periphery. Incidence of occlusive vasculitis ranged from 0% in two studies in switch eyes (Hussain, 2021; Kilani et al., 2021) to 16.7% in one study in switch eyes (Haensli et al., 2021a, 2021b), with visual field loss in one eye (Fukuda et al., 2021). Nowadays, there is better understanding of the importance of early detection and timely management of ocular complications, including educating patients to self-monitor and report symptoms as soon as they arise (Baumal et al., 2021; Holz et al., 2021; Pearce et al., 2022). A follow-up review of the real-world safety of brolucizumab is underway that involves contacting the authors of the published literature for additional, unpublished information and a more systematic collection and assessment of adverse events.

There have been well-described reports of the adverse event profile of brolucizumab including IOI following marketing approval. There is also additional, more systematic information on cases of retinal vasculitis and vascular occlusion (Witkin et al., 2020, 2021). Additionally, safety outcomes from the IRIS Registry and Komodo Healthcare Map, which included 10 654 and 11 161 eyes,

respectively, were published after the systematic searches for the current review were conducted (Khanani, Zarbin, et al., 2022). These show an incidence of approximately 2.4% for IOI and/or vascular occlusion just after the launch of brolucizumab in the USA and during a median follow-up time of approximately 3 months (Khanani, Zarbin, et al., 2022). Physicians are likely since then to have gained increased awareness of these potential risks and the importance of early, intensive management (Baumal, 2022; Baumal et al., 2021), with reports of positive outcomes in such patients (Khoramnia et al., 2022).

Our systematic review provides insights into brolucizumab treatment in everyday clinical practice, in scenarios that may not be assessed in the pivotal trials. It presents a holistic overview across studies that individually can be limited by the small number of included eyes and high between-study heterogeneity. Strengths of the evidence in the current review were that the baseline was well defined, because studies included only new initiators of brolucizumab (either treatment-naïve or switch), and that efficacy parameters were objectively measurable. At review level, strengths included the broad, systematic literature search and retrieval of congress presentations for included congress abstracts. The latter enabled us to capture and include the latest real-world data on brolucizumab, even before they are released as journal publications. A limitation at study level was that the safety outcomes were not always well defined and that there is risk of bias in observational studies that were not designed to measure treatment effect. None of the studies described patient preferences or patient-reported outcomes. Follow-up time points varied widely between studies, making grouping of data challenging. At review level, an important limitation is that several studies included in the main summary were available as congress presentations only, not as full publications, meaning that less information was available for these studies than for the fully published ones.

In conclusion, this summary of real-world data demonstrates the efficacy of brolucizumab in treatment-naïve and previously anti-VEGF-treated patients with nAMD in clinical practice in terms of achievable improvements in visual acuity, CST, IRF and SRF. In addition, reduction of disease activity in anti-VEGF switch eyes was demonstrated by prolongation of the treatment intervals. These observations are in line with those from the pivotal trials in the brolucizumab development programme. Physicians are likely to have gained increased awareness of how best to manage potential risks.

## AUTHOR CONTRIBUTIONS

*Conception and design:* Baumal, Sørensen, Karcher, Freitas, Balez, Clemens, Singer, Kodjikian. *Data collection:* Karcher, Freitas, Becher, Balez, Clemens. *Analysis and interpretation:* Baumal, Sørensen, Karcher, Freitas, Balez, Clemens, Singer, Kodjikian.

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## CONFLICT OF INTEREST

The authors have made the following disclosures. CRB: consultant—Genentech, Novartis, Ora, Regeneron. TLS: None. HK: employee and shareholder—Novartis AG; Editor-in-Chief with yearly honoraria—*Epidemiologic Methods*. RLF: employee and shareholder—Novartis Farma. AB: contractor—Oxford PharmaGenesis. SB: employee and shareholder—Novartis Pharma. AC: employee and shareholder—Novartis AG. MS: consultant—Aerie, Allegro, Allergan, Eyepoint, Genentech, Kodiak, Novartis, Regeneron, Santen; speakers' bureau—Allergan, Genentech, Mallinckrodt, Novartis, Regeneron, Spark; contracted research—Aerie, Allegro, Allergan, DRCR, Genentech, Icon, Ionis, Kalvista, Kodiak, Novartis, Opthea, Optos, Regeneron, Ribomic, Santen, Senju, Sydnexis; equity—Aviceda, Inflammasome, Nanoscope. LK: payment or fees—Alimera/Horus, Allergan/AbbVie, Bayer, Novartis, Roche, Théa.

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## REFERENCES

- Abdin, A.D., Aljundi, W., Weinstein, I., Aljawhari, K., Suffo, S. & Seitz, B. (2021) Intravitreal brolucizumab for treatment of refractory macular edema due to neovascular age-related macular degeneration (real life data) (European Society of Retina Specialists [EURETINA] congress presentation).
- Assi, L., Chamseddine, F., Ibrahim, P., Sabbagh, H., Rosman, L., Congdon, N. et al. (2021) A global assessment of eye health and quality of life: a systematic review of systematic reviews. *JAMA Ophthalmology*, 139, 526–541.
- Aziz, A.A., Khanani, A.M., London, N., Hagen, M.M., Danzig, C.J., Kulkarni, A.D. et al. (2021) Real world efficacy and safety of brolucizumab in neovascular AMD: the REBEL study. *Investigative Ophthalmology & Visual Science*, 62, 451 (Association for Research in Vision and Ophthalmology [ARVO] congress presentation).
- Baumal, C.R. (2022) Risk factors for intraocular inflammation after brolucizumab treatment. *JAMA Ophthalmology*, 140, 28–29.
- Baumal, C.R., Bodaghi, B., Singer, M., Tanzer, D.J., Seres, A., Joshi, M.R. et al. (2021) Expert opinion on management of intraocular inflammation, retinal vasculitis, and vascular occlusion after brolucizumab treatment. *Ophthalmology Retina*, 5, 519–527.
- Baumal, C.R., Spaide, R.F., Vajzovic, L., Freund, K.B., Walter, S.D., John, V. et al. (2020) Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. *Ophthalmology*, 127, 1345–1359.
- Bilgic, A., Kodjikian, L., March de Ribot, F., Vasavada, V., Gonzalez-Cortes, J.H., Abukashabah, A. et al. (2021) Real-world experience with brolucizumab in wet age-related macular degeneration: the REBA study. *Journal of Clinical Medicine*, 10, 2758.
- Bilgic, A., Kodjikian, L., Srivastava, S., Dwivedi, S., Banker, A.S., Abukashabah, A. et al. (2021) Initial pro re nata brolucizumab for exudative AMD: the PROBE study. *Journal of Clinical Medicine*, 10, 4153.
- Book, M., Ziegler, M., Rothaus, K., Faatz, H., Gutfleisch, M., Spital, G. et al. (2022) Erste Erfahrungen mit Brolucizumab bei neovaskulärer altersabhängiger Makuladegeneration und Therapierefraktärität unter der bisherigen Anti-VEGF-Therapie. *Der Ophthalmologe*, 119, 258–264.
- Bulirsch, L.M., Saßmannshausen, M., Nadal, J., Liegl, R., Thiele, S. & Holz, F.G. (2022) Short-term real-world outcomes following intravitreal brolucizumab for neovascular AMD: SHIFT study. *The British Journal of Ophthalmology*, 106, 1288–1294.
- Chakraborty, D., Maiti, A., Sheth, J.U., Boral, S., Mondal, S., Nandi, K. et al. (2021) Brolucizumab in neovascular age-related macular degeneration – Indian real-world experience: the BRAILLE study. *Clinical Ophthalmology*, 15, 3787–3795.
- Cristian, C., Mohla, A., McKibbin, M. & Mukherjee, R. (2021) Early experience of brolucizumab use in a tertiary hospital setting for neovascular age-related macular degeneration (nAMD) (European Society of Retina Specialists [EURETINA] congress presentation).
- Dugel, P.U., Koh, A., Ogura, Y., Jaffe, G.J., Schmidt-Erfurth, U., Brown, D.M. et al. (2020) HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*, 127, 72–84.
- Dugel, P.U., Singh, R.P., Koh, A., Ogura, Y., Weissgerber, G., Gedif, K. et al. (2021) HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*, 128, 89–99.
- Eandi, C.M. & Montesel, A. (2021) Short-term efficacy and safety outcomes of brolucizumab in the real-life clinical practice (European Society of Retina Specialists [EURETINA] congress presentation).
- Enríquez, A.B., Baumal, C.R., Crane, A.M., Witkin, A.J., Lally, D.R., Liang, M.C. et al. (2021) Early experience with brolucizumab treatment of neovascular age-related macular degeneration. *JAMA Ophthalmology*, 139, 441–448.
- Ferris, F.L., Kassoff, A., Bresnick, G.H. & Bailey, I. (1982) New visual acuity charts for clinical research. *American Journal of Ophthalmology*, 94, 91–96.
- Flaxel, C.J., Adelman, R.A., Bailey, S.T., Fawzi, A., Lim, J.I., Vemulakonda, G.A. et al. (2020) Age-related macular degeneration preferred practice pattern®. *Ophthalmology*, 127, P1–P65.
- Fossataro, F., Cozzi, M., Maione, G. & Pece, A. (2021) Structural and vascular features in non-responder neovascular age-related macular degeneration after brolucizumab injection: an optical coherence tomography angiography study (European Society of Retina Specialists [EURETINA] congress presentation).
- Fukuda, Y., Sakurada, Y., Matsubara, M., Hasebe, Y., Sugiyama, A., Kikushima, W. et al. (2021) Comparison of outcomes between 3 monthly brolucizumab and aflibercept injections for polypoidal choroidal vasculopathy. *Biomedicine*, 9, 1164.
- Gohil, R., Crosby-Nwaobi, R., Forbes, A., Burton, B., Hykin, P. & Sivaprasad, S. (2015) Caregiver burden in patients receiving ranibizumab therapy for neovascular age related macular degeneration. *PLoS One*, 10, e0129361.
- Haensli, C., Pfister, I.B. & Garweg, J.G. (2021a) Switching to brolucizumab in eyes incompletely responsive to ranibizumab or aflibercept: real-life 6-month outcomes (European Society of Retina Specialists [EURETINA] congress presentation).
- Haensli, C., Pfister, I.B. & Garweg, J.G. (2021b) Switching to brolucizumab in neovascular age-related macular degeneration incompletely responsive to ranibizumab or aflibercept: real-life 6 month outcomes. *Journal of Clinical Medicine*, 10, 2666.
- Hamou, S.J., Raimondo, C.D., Weber, P. & Woods, B.C. (2021) A retrospective study on the use of brolucizumab for the treatment of NVAMD: a 1-year private practice experience. *Investigative Ophthalmology & Visual Science*, 62, 286 (Association for Research in Vision and Ophthalmology [ARVO] congress presentation).
- Holz, F.G., Figueroa, M.S., Bandello, F., Yang, Y., Ohji, M., Dai, H. et al. (2020) Ranibizumab treatment in treatment-naive neovascular age-related macular degeneration: results from LUMINOUS, a global real-world study. *Retina*, 40, 1673–1685.



- Holz, F.G., Heinz, C., Wolf, A., Hoerauf, H. & Pleyer, U. (2021) Intraokulare Entzündungen bei Brolucizumab-Anwendung. *Der Ophthalmologe*, 118, 248–256.
- Hussain, R. (2021) Real world experience of brolucizumab for persistent macular fluid in neovascular age-related macular degeneration after prior anti-VEGF treatments (American Society of Retina Specialists [ASRS] congress presentation).
- Khanani, A.M., Brown, D.M., Jaffe, G.J., Wyckoff, C.C., Adiguzel, E., Wong, R. et al. (2022) MERLIN: phase 3a, multicenter, randomized, double-masked trial of brolucizumab in participants with nAMD and persistent retinal fluid. *Ophthalmology*, 129, 974–985.
- Khanani, A.M., Zarbin, M.A., Barakat, M.R., Albin, T.A., Kaiser, P.K., Guruprasad, B. et al. (2022) Safety outcomes of brolucizumab in neovascular age-related macular degeneration: results from the IRIS registry and Komodo Healthcare Map. *JAMA Ophthalmology*, 140, 20–28.
- Khoramnia, R., Figueroa, M.S., Hattenbach, L.O., Pavesio, C.E., Anderesi, M., Schmoeder, R. et al. (2022) Manifestations of intraocular inflammation over time in patients on brolucizumab for neovascular AMD. *Graefes Archive for Clinical and Experimental Ophthalmology*, 260, 1843–1856.
- Kilani, A., Vounotrypidis, E., Arrow, S., Reiterer, V., Wertheimer, C. & Wolf, A. (2021) Intravitreal brolucizumab in poor-responsive neovascular age-related macular degeneration (European Society of Retina Specialists [EURETINA] congress presentation).
- Kodjikian, L., Parravano, M., Clemens, A., Dolz-Marco, R., Holz, F.G., Munk, M.R. et al. (2021) Fluid as a critical biomarker in neovascular age-related macular degeneration management: literature review and consensus recommendations. *Eye (London, England)*, 35, 2119–2135.
- Maruko, I., Okada, A.A., Iida, T., Hasegawa, T., Izumi, T., Kawai, M. et al. (2021) Brolucizumab-related intraocular inflammation in Japanese patients with age-related macular degeneration: a short-term multicenter study. *Graefes Archive for Clinical and Experimental Ophthalmology*, 259, 2857–2859.
- Matsumoto, H., Hoshino, J., Mukai, R., Nakamura, K. & Akiyama, H. (2021) Short-term outcomes of intravitreal brolucizumab for treatment-naïve neovascular age-related macular degeneration with type 1 choroidal neovascularization including polypoidal choroidal vasculopathy. *Scientific Reports*, 11, 6759.
- McClard, C.K., Wang, R., Windham, V., Munoz, J., Gomez, S., Fried, S. et al. (2021) Questionnaire to assess life impact of treatment by intravitreal injections (QUALITII): development of a patient-reported measure to assess treatment burden of repeat intravitreal injections. *BMJ Open Ophthalmology*, 6, e000669.
- Montesl, A., Bucolo, C., Sallo, F.B. & Eandi, C.M. (2021) Short-term efficacy and safety outcomes of brolucizumab in the real-life clinical practice. *Frontiers in Pharmacology*, 12, 720345.
- Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D. et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372, n71.
- Pearce, I., Amoaku, W., Bailey, C., Downey, L., Gale, R., Ghanchi, F. et al. (2022) The changing landscape for the management of patients with neovascular AMD: brolucizumab in clinical practice. *Eye (London, England)*, 36, 1–10.
- Rave, V., Sharma, K., Wagner, A. & Kapoor, K. (2021) Real-world analysis of brolucizumab in neovascular AMD. *Investigative Ophthalmology & Visual Science*, 62, 431 (Association for Research in Vision and Ophthalmology [ARVO] congress presentation).
- Reyes-Capo, D.P., Yannuzzi, N.A., Smiddy, W.E. & Flynn, H.W., Jr. (2021) Trends in endophthalmitis associated with intravitreal injection of anti-VEGF agents at a tertiary referral center. *Ophthalmic Surgery, Lasers & Imaging Retina*, 52, 319–326.
- Rispoli, M., Eandi, C.M., Di Antonio, L., Kilian, R., Montesl, A. & Savastano, M.C. (2021) Biomarkers in early response to brolucizumab on pigment epithelium detachment associated with exudative age-related macular degeneration. *Biomedicine*, 9, 668.
- Sharma, A., Kumar, N., Parachuri, N., Sadda, S.R., Corradetti, G., Heier, J. et al. (2021) Brolucizumab-early real-world experience: BREW study. *Eye*, 35, 1045–1047.
- Sharma, K., Rave, V., Wagner, A. & Kapoor, K. (2021) Cost efficacy and challenges of real-world brolucizumab use for neovascular AMD. *Investigative Ophthalmology & Visual Science*, 62, 432 (Association for Research in Vision and Ophthalmology [ARVO] congress presentation).
- Singer, M., Albin, T.A., Seres, A., Bauml, C.R., Parikh, S., Gale, R. et al. (2022) Clinical characteristics and outcomes of eyes with intraocular inflammation after brolucizumab: post hoc analysis of HAWK and HARRIER. *Ophthalmology Retina*, 6, 97–108.
- Sudhalkar, A.A., Kodjikian, L., Bilgic, A., Mathis, T. & Vasavada, S. (2021) Brolucizumab in wet age related macular degeneration and polypoidal choroidal vasculopathy: real world evidence (European Society of Retina Specialists [EURETINA] congress presentation).
- Tadayoni, R., Sararols, L., Weissgerber, G., Verma, R., Clemens, A. & Holz, F.G. (2021) Brolucizumab: a newly developed anti-VEGF molecule for the treatment of neovascular age-related macular degeneration. *Ophthalmologica*, 244, 93–101.
- Walter, S.D. & Saba, N.J. (2021a) Efficacy and durability of brolucizumab in patients being transitioned from prior anti-VEGF therapy (American Society of Retina Specialists [ASRS] congress presentation).
- Walter, S.D. & Saba, N.J. (2021b) Real-world efficacy and safety of brolucizumab. *Investigative Ophthalmology & Visual Science*, 62, 456 (Association for Research in Vision and Ophthalmology [ARVO] congress presentation).
- Witkin, A.J., Hahn, P., Murray, T.G., Arevalo, J.F., Blinder, K.J., Choudhry, N. et al. (2020) Occlusive retinal vasculitis following intravitreal brolucizumab. *Journal of VitreoRetinal Diseases*, 4, 269–279.
- Witkin, A.J., Hahn, P., Murray, T.G., Arevalo, J.F., Blinder, K.J., Choudhry, N. et al. (2021) Brolucizumab-associated intraocular inflammation in eyes without retinal vasculitis. *Journal of VitreoRetinal Diseases*, 5, 326–332.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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