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# Efficacy and safety of brolucizumab versus aflibercept in eyes with polypoidal choroidal vasculopathy in Japanese participants of HAWK

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## ABSTRACT

**Purpose** To compare the efficacy and safety of brolucizumab versus aflibercept in eyes with polypoidal choroidal vasculopathy (PCV) over 96 weeks in the HAWK study.

**Design** HAWK was a global, 2-year, randomised, double-masked, multicentre phase III trial in participants with neovascular age-related macular degeneration.

**Methods** Of the Japanese participants with PCV, 39 received brolucizumab 6 mg and 30 received aflibercept 2 mg. After 3 monthly loading doses, brolucizumab-treated eyes received an injection every 12 weeks (q12w) but were adjusted to q8w if disease activity was detected. Aflibercept-treated eyes received fixed q8w dosing. Mean change in best-corrected visual acuity (BCVA), the proportion of participants on q12w, retinal thickness, retinal fluid changes and safety were assessed to Week 96.

**Results** Mean change in BCVA (early treatment diabetic retinopathy study (ETDRS) letters) from baseline to week 48/week 96 was +10.4/+11.4 for brolucizumab and +11.6/+11.1 for aflibercept. For brolucizumab-treated eyes, the probability of only q12w dosing after loading through week 48 was 76%, and 68% through week 96. Fluid resolution was greater with brolucizumab than aflibercept: respective proportions of eyes with intraretinal fluid and/or subretinal fluid were 7.7% and 30% at week 48 and 12.8% and 16.7% at week 96. Brolucizumab exhibited an overall well-tolerated safety profile despite a higher rate of intraocular inflammation compared with aflibercept.

**Conclusion** In Japanese eyes with PCV, brolucizumab q12w/q8w monotherapy resulted in robust and consistent BCVA gains that were comparable to q8w aflibercept dosing. Anatomical outcomes favoured brolucizumab over aflibercept, with 76% of brolucizumab participants maintained on q12w dosing after loading to week 48.

## INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (nAMD) characterised by polypoidal dilatation and a branching vascular network usually located above the Bruch's membrane and below the retinal pigment epithelium (RPE).<sup>1</sup> The condition is often associated with recurrent subretinal

haemorrhages and fluid accumulation and, if left untreated, can lead to permanent vision loss.<sup>1 2</sup> Indocyanine green angiography (ICGA) remains the diagnostic method of choice for identifying the presence of aneurysmal dilations, the polypoidal lesions characteristic of PCV.<sup>2 3</sup>

PCV is a common subtype of nAMD in Asian populations, in whom the prevalence varies between 22% and 62%.<sup>3 4</sup> Estimates in Caucasian participants have been placed at 7%–10%,<sup>5</sup> but PCV cases are likely to be underdiagnosed in these populations as ICGA is not frequently performed.<sup>6</sup> Indeed, more recent prevalence studies in Caucasians using ICGA have confirmed higher rates between 20% and 31%.<sup>7–9</sup>

PCV is currently managed with intravitreal anti-vascular endothelial growth factor (VEGF) agents alone or in combination with verteporfin photodynamic therapy.<sup>10</sup> However, high treatment and monitoring visit burden remains a challenge, especially in regions where access to treatment is limited.<sup>11</sup> Effective treatments that prolong intervals between injections, while maintaining vision gains, remain an important unmet need.

Brolucizumab is a single-chain antibody fragment that has a high affinity for VEGF. Its low molecular weight (26 kDa) allows the delivery of more drug per injection compared with other available anti-VEGFs and offers the potential for more effective tissue penetration and increased duration of action.<sup>12</sup> In the 2-year phase III HAWK and HARRIER studies, there were comparable best-corrected visual acuity (BCVA) gains and superior anatomical outcomes with brolucizumab 6 mg administered every 12 weeks (q12w) with the option to adjust to every 8 weeks (q8w) if disease activity was detected, when compared with a fixed q8w aflibercept treatment regimen. Moreover, after 3 monthly loading doses, over 50% of brolucizumab, 6 mg-treated eyes were maintained on a q12w dosing interval over 48 weeks.<sup>13 14</sup> In this HAWK study subanalysis, we report the visual acuity and anatomic results of brolucizumab compared with aflibercept treatment in eyes with PCV.

## METHODS

### Study design

HAWK (NCT02307682) was a prospective, 2-year, randomised, double-masked, multicentre phase III

trial conducted at multiple sites in the USA, Australia, Japan, Canada, Israel, New Zealand, Argentina, Colombia, Mexico and Panama from December 2014 to March 2018. The study adhered to the tenets of the Declaration of Helsinki, International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guidelines and other regulations as applicable and was reported with the Health Insurance Portability and Accountability Act of 1996. The protocol was approved by an Independent Ethics Committee/Institutional Review Board at each study site, and all study participants provided written informed consent. The trial protocol and statistical analysis plan have been previously published.<sup>13</sup>

### Trial participants

Eligible participants were aged  $\geq 50$  years, had study eye: intraretinal fluid (IRF) and/or subretinal fluid (SRF) affecting the central subfield as assessed on spectral domain optical coherence tomography (OCT); BCVA between 78 and 23 early treatment diabetic retinopathy study (ETDRS) letters (inclusive; Snellen equivalents, approximately 20/32 to 20/400) and no fibrosis or geographic atrophy affecting the central subfield. Participants who received any approved or investigational nAMD treatment at any time (study eye) were excluded. The detailed eligibility criteria for the study are described in the primary publication.<sup>13</sup> Screening visit ICGA images from all eyes of Japanese participants enrolled from 34 study centres in Japan were further assessed by certified readers at the Duke Reading Center (Durham, North Carolina, USA) for the presence or absence of PCV using a Heidelberg HRA system. A study eye movie was obtained that captured transit of ICG dye according to the following parameters: 30° macula-centred image field, 100% power, movie max, high speed. In addition, macula-centred still images were obtained on study and fellow eyes at 1.5, 3 and 6 min post-ICG injection. Polyps were identified as round or ovoid hyperfluorescent structures approximately 50 microns or larger. The subgroup with PCV, as evidenced by visible polyps on ICGA, was used for this subanalysis.

### Randomisation and treatment

In HAWK, eyes were randomised 1:1:1 to brolocizumab 3 mg (n=358), 6 mg (n=360) or aflibercept 2 mg (n=360). Randomisation and treatment masking were as previously described.<sup>13</sup> Eyes were not stratified by PCV status. Following 3 monthly loading doses at weeks 0, 4 and 8, brolocizumab study eyes were given an intravitreal injection q12w, which was adjusted to q8w for the remainder of the study period if disease activity was detected at any of the predefined assessment visits; aflibercept was dosed q8w, as per label (online supplemental figure S1). Disease activity assessments (DAAs) were performed by the masked investigator at weeks 16–20, and thereafter at scheduled q12w treatment visits (Weeks 32, 44, 56, 68, 80 and 92). The protocol provided DAA guidance; however, the final treatment decision was made by the masked investigator based on their own clinical judgement. Treatment exposure was identical up to week 16, allowing a matched comparison of brolocizumab and aflibercept up to 8 weeks after loading.

### Endpoints and statistical analyses

For the global HAWK study, the primary analysis was performed at week 48 and final analysis at week 96. The study endpoints for this subanalysis include BCVA change from baseline up to week 96; q12w treatment status at weeks 48 and 96 and q12w treatment status at weeks 48 and 96 in eyes with no q8w need during

the first q12w cycle; status of IRF and/or SRF and sub-RPE fluid up to week 96; mean reduction and absolute values of central subfield thickness (CST) from baseline up to week 96; and safety endpoints including incidence of treatment-emergent ocular and nonocular adverse events (AEs) and serious AEs (SAEs).

The small sample size for this subgroup analysis was not powered to make any inferential analysis; hence, only descriptive statistics are presented. As in the global HAWK study, the change in BCVA from baseline, CST and the presence of IRF, SRF and sub-RPE fluid in the study eye were assessed using the full analysis set (FAS) with the last observation carried forward approach for imputing missing data.<sup>13</sup> Efficacy assessments performed after a subject discontinued study treatment and started standard of care were censored. The FAS comprised all participants from the subgroup of PCV participants who were assigned to a treatment regimen and received at least one intravitreal injection. The probabilities for maintaining q12w status were derived from time-to-event analyses (first disease activity/q8w need). In case of informative censoring (lack of efficacy or safety), a q8w need was imputed.

### Brolocizumab Safety Review Committee

In early 2020, following postmarketing reports of vasculitis, including retinal occlusive vasculitis, associated with intraocular inflammation (IOI) with brolocizumab, Novartis convened an external Safety Review Committee (SRC) to provide an independent review of these cases and a comparison with events seen in the HAWK and HARRIER trials.<sup>15</sup> The SRC performed an unmasked post hoc review of all cases of investigator-reported IOI (including the case of perivascular sheathing), retinal vascular occlusions and endophthalmitis, including those occurring in the Japanese participants with PCV.

## RESULTS

### Patient population

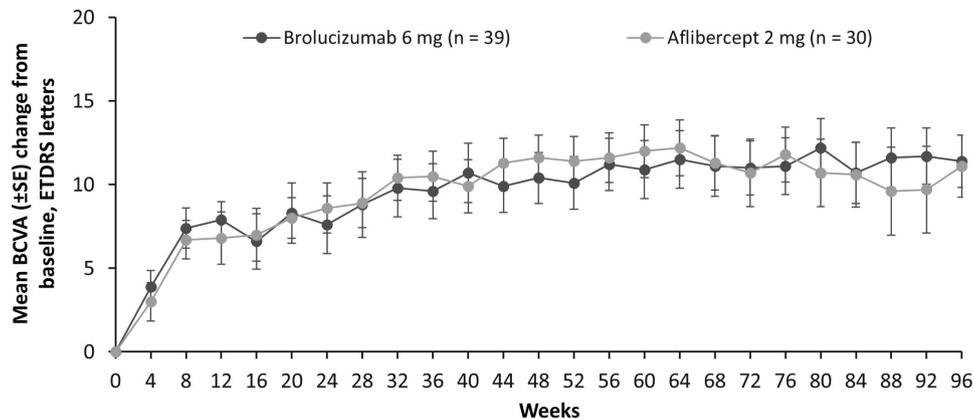
Of the 152 Japanese participants enrolled in the HAWK study, 89 (59%) participants were diagnosed with PCV at screening (brolocizumab 3 mg (n=20), 6 mg (n=39), aflibercept 2 mg (n=30)). As brolocizumab 6 mg is the approved dose for the treatment of nAMD, the brolocizumab 3 mg results will not be discussed here. Overall, the baseline characteristics were balanced between the treatment arms among the Japanese participants with PCV (table 1) apart from the mean CST value, which was approximately 50  $\mu\text{m}$  lower in the brolocizumab 6 mg arm. Mean baseline BCVA in the eyes with PCV was 62.4 ETDRS letters in both treatment arms (table 1).

**Table 1** Demographic and baseline ocular characteristics of Japanese participants with PCV

Characteristic	Brolocizumab 6 mg (n=39)	Aflibercept 2 mg (n=30)
BCVA, letters, mean (SD)	62.4 (13.9)	62.4 (10.8)
CST, $\mu\text{m}$ , mean (SD)	392.8 (96.1)	444.8 (129.0)
Presence of IRF and/or SRF, n (%)	37 (94.9)	26 (86.7)
Presence of sub-RPE fluid, n (%)	23 (59.0)	16 (53.3)
CNV-associated lesion area, $\text{mm}^2$ , mean (SD)	4.4 (4.1)	4.9 (4.0)

All randomised analysis set.

BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; CST, central subfield thickness; IRF, intraretinal fluid; PCV, polypoidal choroidal vasculopathy; RPE, retinal pigment epithelium; SRF, subretinal fluid.



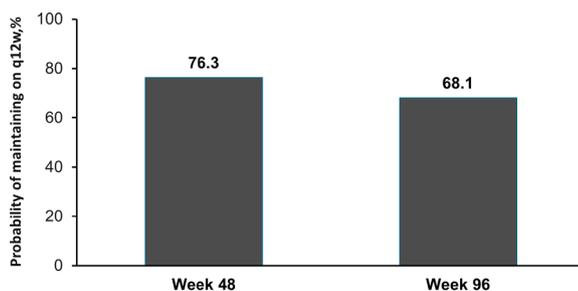
**Figure 1** Mean BCVA change from baseline to Week 96 in Japanese participants with PCV. BCVA, best-corrected visual acuity; PCV, polypoidal choroidal vasculopathy.

### Visual acuity outcomes

Robust BCVA gains were observed in eyes with PCV across the treatment arms (figure 1). At the primary endpoint at week 48, the mean change in BCVA from baseline (mean BCVA in parentheses) was +10.4 (72.7) letters for brolucizumab 6 mg, and +11.6 (73.9) letters for aflibercept 2 mg. These visual gains were maintained to week 96 with a mean change in BCVA from baseline of +11.4 (73.7) letters for brolucizumab 6 mg, and +11.1 (73.5) letters for aflibercept 2 mg (figure 1).

### Status of q12w treatment

The BCVA gains were achieved with the majority of brolucizumab-treated participants maintained on a q12w regimen after the loading phase. For brolucizumab 6 mg-treated eyes with PCV, the probability (Kaplan–Meier estimate) for exclusively maintaining on a q12w dosing interval after loading through week 48 was 76% and through week 96 was 68% (figure 2). Furthermore, if a brolucizumab



Parameter	Brolucizumab 6 mg (n = 39)
Positive q12w treatment status at Week 48 among those with no q8w need during the first q12w cycle, %	93.5
Positive q12w treatment status at Week 96 among those with no q8w need during the first q12w cycle, %	86.0
Positive q12w treatment status at Week 96 among those with no q8w need up to Week 48, %	89.3

**Figure 2** Upper panel: Percentage of brolucizumab 6 mg-treated Japanese eyes with PCV on an exclusive q12w dosing interval through week 48 and week 96. Lower panel: Probability of eyes with PCV remaining on a q12w interval up to week 48 and week 96. Estimated percentages from Kaplan–Meier analysis with ‘Efficacy/Safety approach’. In case of missing/confounded data due to lack of efficacy and/or safety a ‘q8-need’ is allocated, otherwise censoring is applied. q12w, 12 week dosing interval; PCV, polypoidal choroidal vasculopathy.

6 mg-treated participant with PCV successfully completed the first q12w interval (ie, week 8–week 20), the probability of remaining on a q12w interval until week 48 increased to 94% and until week 96 to 86%. Similarly, brolucizumab 6 mg-treated participants with PCV who successfully completed week 48 on a q12w interval had an 89% of probability remaining on a q12w interval until week 96.

### Anatomic outcomes

#### Fluid status

At week 4, after the first injection, IRF and/or SRF was present in fewer brolucizumab 6 mg-treated eyes than aflibercept-treated eyes (48.7% vs 70%, respectively). This difference was seen early in the matched phase to week 16 (brolucizumab 6 mg, 35.0% vs aflibercept, 43.3%) and the maintenance phase to week 96 (brolucizumab 6 mg, 12.8% vs aflibercept, 16.7%; figure 3A).

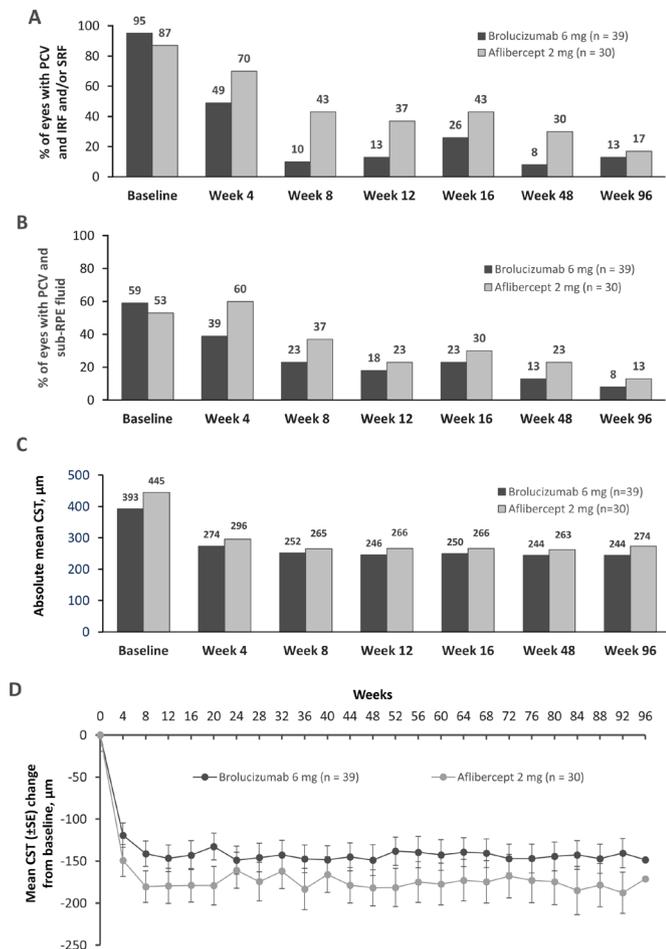
Similarly, fewer eyes had sub-RPE fluid in the brolucizumab 6 mg-treated arm compared with the aflibercept-treated arm from week 4 (38.5% vs 60.0%) to week 96 (7.7% vs 13.3%, respectively; figure 3B).

#### CST changes

The absolute mean CST at week 16 in the brolucizumab 6 mg arm was 250  $\mu\text{m}$  (baseline mean CST, 393  $\mu\text{m}$ ) and 266  $\mu\text{m}$  (baseline mean CST, 445  $\mu\text{m}$ ) for aflibercept 2 mg; at week 48, the absolute mean CST values were 244  $\mu\text{m}$  for brolucizumab and 263  $\mu\text{m}$  for aflibercept and at week 96 were 244  $\mu\text{m}$  and 274  $\mu\text{m}$ , respectively (figure 3C). The mean CST ( $\pm$ SE) reduction from baseline at week 16 was 143 ( $\pm$ 16)  $\mu\text{m}$  for brolucizumab 6 mg and 179 ( $\pm$ 21)  $\mu\text{m}$  for aflibercept 2 mg; at week 48, the respective mean CST ( $\pm$ SE) reductions were 149 ( $\pm$ 17)  $\mu\text{m}$  and 182 ( $\pm$ 21)  $\mu\text{m}$ . The CST reductions at week 48 were maintained at week 96 (figure 3D).

### Safety outcomes

The safety profile of brolucizumab in participants with PCV was similar to that observed in the overall HAWK population, and, in general, brolucizumab was well tolerated (table 2). The most common ocular AEs in each arm were cataract (brolucizumab 6 mg; 12.8% (n=5)) and conjunctivitis allergic (aflibercept; 10% (n=3)). Ocular SAEs were cataract (2.6% (n=1)) in the brolucizumab 6 mg arm and macular hole (3.3% (n=1)) in the aflibercept arm. A higher incidence of IOI events was reported in the brolucizumab arm (15.4% (n=6)) compared with none in the aflibercept arm; two were reported as uveitis, two as iritis, one



**Figure 3** (A) Proportion of eyes with PCV and IRF and/or SRF. All eyes had fluid at screening; (B) proportion of eyes with PCV and sub-RPE fluid; (C) and (D) mean CST change and absolute CST values up to Week 96 in eyes of Japanese participants with PCV. CST, central subfield thickness; IRF, intraretinal fluid; PCV, polypoidal choroidal vasculopathy; RPE, retinal pigment epithelium; SRF, subretinal fluid.

as anterior chamber inflammation and one was a case of perivascular sheathing. One of these participants was also reported as having a branch retinal artery occlusion (BRAO). Three of the participants continued the study treatment, whereas in the other three, brolucizumab was withdrawn. For the final BCVA of these six participants with an IOI, three gained  $\geq 15$  letters of vision (one of whom was the participant with BRAO), one gained 10 letters, one had no change compared with baseline and one had a BCVA loss of  $-4$  letters at end of study. The average BCVA gains of the participants with IOI and PCV were  $+9.8$  letters, which is similar to the overall PCV cohort. AEs are presented by incidence in table 2 and further details of the IOI events including treatment, timings and outcome are presented in online supplemental table 1.

Following their review of the post-marketing cases and the phase III studies, the SRC identified a spectrum of inflammatory signs ranging from IOI to retinal vasculitis to retinal vascular occlusion that sometimes resulted in visual acuity loss.<sup>15</sup> In the six participants with PCV and investigator-reported IOI, the SRC identified signs of retinal vasculitis in five of the six study eyes (four definite, one probable) and of these five study eyes, two developed retinal vascular occlusion (one probable; online supplemental table 1).

**Table 2** Overall and ocular safety data of Japanese participants with PCV

Adverse event	Brolucizumab 6 mg (n=39)	Aflibercept 2 mg (n=30)
Participants with $\geq 1$ adverse event, n (%) <sup>*</sup>		
Ocular (study eye)	22 (56.4)	12 (40.0)
Nonocular	34 (87.2)	24 (80.0)
Participants with $\geq 1$ serious adverse event, n (%) <sup>*</sup>		
Ocular (study eye)	1 (2.6)	1 (3.3)
Nonocular	7 (17.9)	7 (23.3)
Participants with $\geq 15$ letter loss from baseline at week 96, n (%) <sup>†</sup>		
Ocular (study eye)	0 (0.0)	0 (0.0)
Participants with $\geq 1$ nonocular arterial thromboembolic event, n (%) <sup>*</sup>		
Death, n (%)	0 (0.0)	0 (0.0)
Ocular AEs ( $\geq 5\%$ ), preferred term, n (%) <sup>†</sup>		
Participants with $\geq 1$ event		
Cataract	5 (12.8)	1 (3.3)
Intraocular pressure increased	4 (10.3)	2 (6.7)
Conjunctival haemorrhage	3 (7.7)	2 (6.7)
Eye pain	3 (7.7)	1 (3.3)
Conjunctivitis	3 (7.7)	0 (0.0)
Dry eye	2 (5.1)	1 (3.3)
Retinal haemorrhage	2 (5.1)	1 (3.3)
Retinal tear	2 (5.1)	0 (0.0)
Vitreous detachment	1 (2.6)	0 (0.0)
Trichiasis	1 (2.6)	0 (0.0)
Conjunctivitis allergic	0 (0.0)	3 (10.0)
Glaucoma	0 (0.0)	0 (0.0)
Intraocular inflammation, retinal arterial occlusive event and endophthalmitis AEs, n (%) <sup>†*</sup>		
Uveitis	2 (5.1)	0 (0.0)
Iritis	2 (5.1)	0 (0.0)
Anterior chamber inflammation	1 (2.6)	0 (0.0)
Retinal artery occlusion	1 (2.6)	0 (0.0)
Retinal perivascular sheathing	1 (2.6)	0 (0.0)
Endophthalmitis	0 (0.0)	0 (0.0)

Medical Dictionary for Regulatory Activities Version 20.1 has been used for the reporting of adverse events. Safety Analysis Set.

<sup>\*</sup>AEs with a start date on or after the date of first study treatment administration were counted. A participant with multiple occurrences of an AE for a preferred term or system organ class was counted only once in each specific category.

<sup>†</sup>Ocular AEs  $\geq 5\%$  in any treatment arm in the study.

<sup>‡</sup>Selected for incidence  $>2\%$  in either study and/or clinician interest.

AE, adverse event; PCV, polypoidal choroidal vasculopathy.

## DISCUSSION

A major goal of PCV management is to achieve optimal visual outcomes through control of disease activity while reducing treatment and monitoring visit burden.<sup>16</sup> This subanalysis shows that overall robust BCVA gains were achieved with brolucizumab q12w/q8w treatment over 96 weeks that were comparable with aflibercept treatment on a fixed q8w dosing. Anatomical outcomes, as determined by fluid resolution, favoured brolucizumab treatment over aflibercept.

Anatomical measures that include CST and retinal fluid on OCT are considered to be important indicators of active disease in nAMD and PCV management.<sup>17</sup> Here, a higher proportion of eyes with PCV that were treated with brolucizumab 6 mg had IRF and/or SRF and sub-RPE fluid resolution compared with

those treated with aflibercept. This fluid resolution could signify that polyps are rendered inactive, a definition also employed in other PCV treatment trials. Notably, the greater fluid resolution in brolocizumab-treated eyes with PCV was evident after the first dose (week 4), through the matched phase and at weeks 48 and 96. At both of these later time points, the majority of brolocizumab-treated eyes was on a q12w treatment regimen compared with q8w for the aflibercept arm. Given that residual retinal fluid may suggest suboptimal control of disease activity,<sup>10 18</sup> the ability of brolocizumab monotherapy to resolve fluid in a higher percentage of eyes suggests that it may be an effective alternative treatment option to combination therapy for participants with PCV. There were notable CST reductions during the loading phase (to week 12) in both brolocizumab and aflibercept treatment arms, and these comparable improvements were maintained up to week 96 despite the lower baseline CST in the brolocizumab 6 mg arm.

Overall, 76% of the brolocizumab 6 mg group were maintained on an exclusive q12w dosing interval following the loading phase through week 48 and 68% through week 96. It is important to note that these participants were on a q12w treatment interval immediately following loading and successfully completed three q12w cycles up to week 48 and seven q12w cycles up to week 96. By contrast, in other studies investigating conventional treat-and-extend (T&E) regimens, successive treatment extensions are done postloading and the proportions of participants reaching a q12w interval at week 52 and week 96 are generally reported. Brolocizumab-treated participants adjusted to a q8w interval as a result of disease activity could not also be extended to q12w, which differs from T&E studies where treatment intervals can be extended again following a decrease. In the participants with PCV in HAWK, the dosing interval through the first 12-week treatment interval was highly predictive of the subsequent dosing interval. Among eyes that successfully completed the first q12w interval, there was 94% probability that they could remain on brolocizumab q12w dosing up to week 48 and 86% probability through week 96. In clinical practice, these robust predictability results should help physicians to confidently determine the patients who are suitable for brolocizumab q12w dosing soon after the loading phase, thus providing an efficient treatment scheduling approach.

A higher incidence of IOI events was reported in the brolocizumab arm compared with aflibercept treatment, although the rate of 15.4% should be viewed with caution due to the small subgroup analysed. These IOI cases in the eyes with PCV have to be interpreted in the context of postmarketing cases of vasculitis and retinal occlusive vasculitis that have been reported in relation to the use of brolocizumab. A retrospective, unmasked review by an independent SRC of the HAWK and HARRIER participants with IOI events has revealed evidence of retinal vasculitis and vascular occlusion on images.<sup>15</sup> While there were no cases of moderate or severe vision loss related to the IOI events seen in the HAWK PCV subpopulation, physicians should consider this risk prior to initiating treatment with brolocizumab. If inflammation is identified, perform wide field imaging exams to rule out vasculitis and retinal occlusion. Additional brolocizumab injections should be withheld and the inflammation should be treated as per standard clinical practice according to the severity of the event.<sup>19</sup>

This is the first analysis of the safety and efficacy of brolocizumab in eyes with PCV. The involvement of the Central Reading Center during the screening phase ensured that only participants with well-defined PCV were included. This study also has limitations. The analysis was exploratory, and the number of eyes

in each treatment arm is small; hence, it was not powered to perform comparative statistics between the treatment groups nor was the HAWK study designed to directly compare outcomes in eyes with PCV to those without PCV. Furthermore, eyes of Japanese participants were not stratified according to PCV status, as identified by ICGA imaging. However, apart from mean CST, there were no imbalances in baseline characteristics observed between the eyes with PCV in the treatment arms and when compared with the overall HAWK population.<sup>13 14</sup> It was also not possible to evaluate the effect of brolocizumab on polyp regression as ICGA was only performed at screening, and not at follow-up visits. However, the presence of IRF and/or SRF in fewer brolocizumab 6 mg-treated eyes compared with aflibercept-treated eyes may indicate a higher proportion of participants with inactive polyps.

In conclusion, robust BCVA gains and greater fluid resolution over 96 weeks were observed in eyes treated with brolocizumab q12w/q8w monotherapy compared with those treated with fixed q8w aflibercept dosing. These visual and anatomic outcomes were achieved through week 48 with 76% of brolocizumab 6 mg participants maintained on a q12w interval after loading. There will be a growing need to manage eyes with PCV in many parts of the world, particularly in Asia where prevalence is high, as the population becomes increasingly aged. The results from this analysis suggest that brolocizumab could help to alleviate the treatment burden associated with PCV.

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**Correction notice** This paper has been corrected since it was published online. A change to the text was introduced during copy-editing and we have reinstated the original wording.

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