Prospective exploratory study to assess the safety and efficacy of afibercept in cystoid macular oedema associated with retinitis pigmentosa

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ABSTRACT

Aims To report the safety and efficacy of intravitreal afibercept (Eylea) (ivA) for retinitis pigmentosa-associated cystoid macular oedema (RP-CMO) at 12 months via mean central macular thickness (CMT) and reported adverse events.

Methods A prospective, exploratory, phase II, non-randomised, single-centre, open-label, 1-arm clinical trial involving 30 eyes of 30 patients. Serial ivA was given via loading dose (three injections) followed by treat and extend protocol over 12 months.

Results Twenty-nine out of 30 (96.7%) patients completed 12 months of follow-up. A total of four to 11 injections per patient were given over the 12 month study. No statistically significant reduction of CMT or visual acuity (VA) improvement was demonstrated in the group overall. Eleven out of 29 (37.9%) participants were considered as ‘responders’, demonstrating at least an 11% reduction of CMT at 12 months on spectral domain optical coherence tomography compared with baseline. A reduction of CMT by mean (SD) 28.1% (12.9%) was observed in responders at 12 months, however, no statistically significant corresponding improvement in best corrected VA was seen. Baseline characteristics were similar between responder and non-responder groups. No clinically significant adverse events were deemed secondary to ivA.

Conclusion This first prospective exploratory study demonstrates both the safety and acceptability of serial ivA in patients with RP-CMO, effective at reducing CMT in 37.9% of patients. All patients demonstrating anatomical response did so after their first injection. Longer duration of CMO did not negatively affect response to anti-VEGF. Further study in a larger cohort of patients with shorter CMO duration would be valuable to better establish the utility of VEGF blockade in RP-CMO.

Trial registration numbers EudraCT (2015-003723-65); ClinicalTrials.gov (NCT02661711).

INTRODUCTION

Inherited retinal disease is the second most common cause of visual loss in childhood and the most common cause of visual loss in the working age population.1 Retinitis pigmentosa-associated cystoid macular oedema (RP-CMO) is a known complication of retinitis pigmentosa (RP), reported to occur in 10%–50% of patients with RP across their lifetime.2-5 One of the most commonly reported ocular symptoms of RP is relentless and progressive concentric peripheral visual field loss for which there is currently no cure. Complications of RP such as cataract and RP-CMO interfere with central vision and are thereby particularly debilitating, making effective treatments for RP-CMO highly valuable.

Several mechanisms have been proposed to explain RP-CMO, however, no single aetiology has been definitively established.6 These include: (i) breakdown of the blood-retinal barrier,7,8 (ii) failure (or dysfunction) of the retinal pigment epithelium (RPE) pump mechanism,9 (iii) Müller cell oedema and dysfunction,10 (iv) anti-retinal antibodies11 and (v) vitreous traction.12-13 Treatment approaches for RP-CMO have included: laser therapy, topical carbonic anhydrase inhibitors (CAIs), oral CAIs, pericellular and intravitreal steroids, and intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents.6 The vast majority of the published literature is retrospective, however, involving only small numbers of patients with short duration of follow-up. RP-CMO has been associated with younger age but not with gender.14 RP-CMO is most prevalent in patients with autosomal dominant (AD) inheritance (71.4% with CMO in at least one eye), followed by autosomal recessive (AR)/sporadic inheritance (58.9%) and X-linked (XL) inheritance (12.5%).14 Patients with epiretinal membrane (ERM) and cataract/pseudophakia are less likely to develop CMO.14

The current mainstay of treatment for RP-CMO is topical/oral CAIs, however, there is no level 1 evidence supporting their use and studies have demonstrated highly variable efficacy. Liew et al carried out a 12 month retrospective review of 81 patients with RP-CMO at Moorfields Eye Hospital, UK treated with topical dorzolamide (64 patients, 125 eyes) or oral acetazolamide (17 patients, 32 eyes).15 Forty per cent of eyes (53.1% of patients) following treatment with topical dorzolamide and 28.1% of eyes (41.2% of patients) following treatment with oral acetazolamide demonstrated response (defined as a reduction of central macular thickness (CMT) on optical coherence tomography (OCT) of at least 11% between visits).15 A cross-sectional study performed on this same cohort of patients (n=81) identified older age, earlier age of onset of symptoms, and thicker CMT to be associated with lower visual acuity (VA). Gender and inheritance pattern were not found to be associated with VA.16

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Several publications have observed a variable effect of anti-VEGFs in RP-CMO, including: pegaptanib sodium (Macugen, OSI Eyetech Pharmaceuticals/Pfizer, New York, New York, USA),17 bevacizumab (Avastin, Genentech/Roche, South San Francisco, California, USA),18 19 ranibizumab (Lucentis; Genentech, South San Francisco, California, USA)20 21 and aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, New York, New York, USA) and Bayer Healthcare Pharmaceuticals, Berlin, Germany).22 23 The largest study to date by Artunay et al enrolled 30 eyes of 30 patients with RP-CMO refractory to treatment with oral acetazolamide for at least 6 months.20 Fifteen eyes of 15 patients were treated with a single intravitreal injection of ranibizumab (ivR). Fifteen eyes of 15 patients that declined ivR were used as a control group. Thirteen out of 15 eyes (87%) in the treatment group demonstrated significant reduction of CMO at 6 months post-injection, although the definition of ‘significant reduction’ is not stated in the paper. No statistically significant difference in VA was demonstrated in this cohort as a whole, or in subgroup analysis of responders. Moustafa and Moschos published a case report demonstrating improvement of CMT and VA following a single unilateral intravitreal injection of aflibercept (ivA) in a 52-year-old with RP-CMO. At baseline, vision was 3/10. One month post-injection, vision improved to 4/10 and CMO resolved. Documented visual improvement was maintained at both 2-month and 6-month reviews.22 Our group subsequently published a case report regarding a 38-year-old patient with a 3-year history of bilateral RP-CMO. Previous treatment had been with topical 2% dorzolamide, oral acetazolamide, and ivR, which had demonstrated only minimal reduction of CMO. He had a good structural response to bilateral doses of ivA. He subsequently received serial ivR with further reduction of CMT observed. VA remained stable throughout.21

Given the aforementioned lack of high quality evidence for use of therapeutic options for RP-CMO, we designed a phase II exploratory prospective study to assess the safety and efficacy of ivA in a well-characterised cohort of patients with RP-CMO in order to help provide evidence towards this unmet medical need.

METHODS
Written informed consent was obtained from all patients. The study was undertaken at Moorfields Eye Hospital NHS Foundation Trust, UK. The consort flow diagram illustrating flow of patients throughout the study can be found in online supplementary figure 1.

Identification of suitable patients for the trial
An electronic search was performed to identify all patients seen at Moorfields Eye Hospital NHS Foundation Trust, UK, between 1st December 2012 and 30th November 2015 with the phrases ‘retinitis pigmentosa’ and ‘cystoid macular oedema’ appearing in their electronic patient records. This initial search identified 295 patients; however, after review of each electronic patient record and latest Spectral domain OCT (SDOCT) imaging, 165 patients were excluded from the study for the following reasons: no/ minimal CMO (111), visually significant ERM (17), VA too poor (24), VA too good (4), macular hole (2), visually significant cataract (2), under 16 years of age (4) and pregnant (1). Please refer to online supplementary information 1 for a list of inclusion/exclusion criteria.

A total of 130 patients were therefore found to be potentially suitable participants. Patients were contacted by the dedicated trial fellow (SAS) at their routine medical retina clinic or by telephone/letter. The aims, methods, anticipated benefits and potential hazards of the study were explained to each patient and a patient information sheet provided. Patients were given a minimum of 24 hours to consider whether they wished to attend a baseline evaluation/screening visit. Of these patients: 18 could not be contacted/did not reply, 1 was deceased, 32 wished to be considered for the study, and 79 declined to participate for reasons including: did not want intravitreal injections (n = 42), happy with their current treatment and/or vision (n = 22), or unable to commit to the study visits (due to distance from the hospital or concerns about the impact it would have on their job) (n = 15).

Out of 32 patients who wished to be considered for the study, 15 patients were being treated with a topical CAI (dorzolamide or brinzolamide) and five patients were being treated with an oral CAI (acetazolamide) at time of contact. Patients were requested to stop using CAIs for at least 1 month in the study eye if being used topically, or at least 3 months if orally, before their screening appointment was made. Ten patients were not using any treatment. Two patients had no CMO at screening so were excluded from the trial.

Recruitment period
All 30 patients were recruited over a 6-month period.

Baseline evaluation/screening visit
At the screening appointment, each patient had the opportunity to ask further questions before written informed consent was taken. Baseline tests of visual function can be found in online supplementary information 2.

If a patient was deemed eligible to enter the trial, intra-ocular pressure (IOP) was measured using Goldmann tonometry and their first ivA was given that day (‘Visit 1’). The IOP was re-checked 30 min after ivA, and appropriate treatment commenced if IOP was increased (>30 mm Hg).

Randomisation
The study consisted of only one-arm and all trial patients received the active drug, aflibercept via intravitreal injection.

Follow-up visits
At each follow-up visit, patients had their vital signs checked and a medication review performed. Tests of visual function carried out at every visit, included: best corrected VA (BCVA), colour vision, contrast sensitivity and SDOCT. In addition, microradiometry and fundus autofluorescence were undertaken at the 6-month and 12-month (exit) visits. IvA was administered every 4 weeks for the first 3 months (loading phase), followed by a treat and extend protocol up to 12 months. Extension from monthly to 6, 8, 10 and 12 week follow-up occurred when there was no reduction in macular oedema compared with the previous visit. Please refer to online supplementary table 1 for a schedule of assessments and online supplementary information 3 for description of the intravitreal procedure.

Primary outcome measures
There were two primary outcome measures: (i) To report the safety of aflibercept in RP-CMO throughout the study via the documentation of adverse events (AEs) deemed related to the trial drug; (ii) To report the efficacy of aflibercept in RP-CMO via mean CMT on SDOCT at 12 months after baseline.
RESULTS
Baseline characteristics and injection frequency for all participants are summarised in supplementary tables 2–6 and supplementary information 6.

Outcome measures
Efficacy: analysis of all study participants
The primary and secondary efficacy outcomes for all patients (responders and non-responders) within the study are summarised in tables 1 and 2. Mean CMT at 12 months was 413.4 µm (SD 98.2 µm, 95% CI 376.0 to 450.7 µm), corresponding to a reduction in CMT of 47.6 µm (SD 86.6 µm, 95% CI –80.5 to –14.6 µm) or 9.61% (17.56%) between baseline and 12 months. Mean macular volume at 12 months was 8.0 mm³ (SD 0.7, 95% CI 7.7 to 8.2), corresponding to a change in macular volume of –0.3 mm³ (SD 0.7, 95% CI –0.6 to –0.1) between baseline and 12 months. Mean CMT at 6 months was similar at 414.8 µm (SD 96.4 µm, 95% CI 378.1 to 451.4 µm), corresponding to a reduction in CMT of 46.2 µm (SD 108.7 µm, 95% CI –87.6 to –4.9 µm) or 8.13% (23.3%) (see supplementary figure 2) between baseline and 6 months. Mean macular volume at 6 months was 7.9 mm³ (SD 0.6, 95% CI 7.7 to 8.2), corresponding to a change in macular volume of –0.3 mm³ (SD 0.8, 95% CI –0.7 to 0.0) between baseline and 6 months.

Mean ETDRS BCVA was 66.9 letters (SD 10.6, 95% CI 62.8 to 70.9) at 6 months and 68.0 letters (SD 11.1, 95% CI 63.8 to 72.3) at 12 months. This equated to a gain of 3.1 letters (SD 6.6, 95% CI 0.6 to 5.6) and 4.3 letters (SD 6.9, 95% CI 1.7 to 6.9) respectively at 6 and 12 months (see supplementary figure 3). No patients lost ≥30 letters.

Mean retinal sensitivity at 6 months was 4.92 dB (SD 3.49, 95% CI 3.56 to 6.27), corresponding to a change in retinal sensitivity of –1.23 dB (SD 2.24, 95% CI –2.1 to –0.37). Data were missing for 2 (6%) patients. Mean retinal sensitivity at 12 months was 4.93 dB (SD 3.48, 95% CI 3.55 to 6.31), corresponding to a change in retinal sensitivity of –1.09 dB (SD 2.10, 95% CI –1.9 to –0.27). Data were missing for 2 (6%) patients.

Table 1 Primary outcome measures

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Aflibercept (n=29)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central macular thickness on SD-OCT (µm), mean (SD) at baseline</td>
<td>458.7 (84.6)</td>
<td></td>
</tr>
<tr>
<td>Change in central macular thickness on SD-OCT (µm) from baseline to 12 months</td>
<td>413.4 (98.2)</td>
<td>376.0 to 450.7</td>
</tr>
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</table>

Table 2 Secondary outcome measures

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Eylea (n=29)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central macular thickness on SD-OCT (µm), mean (SD) at 6 months</td>
<td>414.8 (96.4)</td>
<td>378.1 to 451.4</td>
</tr>
<tr>
<td>Change in ETDRS BCVA (letters), mean (SD) from baseline to 12 months</td>
<td>4.3 (6.9)</td>
<td>1.7 to 6.9</td>
</tr>
<tr>
<td>Macular volume on SD-OCT (mm³), mean (SD) at 12 months</td>
<td>8.0 (0.7)</td>
<td>7.7 to 8.2</td>
</tr>
</tbody>
</table>

Macular volume on SD-OCT (mm³), mean (SD) at 12 months:

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eylea</td>
<td>8.0 (0.7)</td>
<td>7.7 to 8.2</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>414.8</td>
<td>378.1 to 451.4</td>
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</table>

Retinal sensitivity (dB), mean (SD) at 6 months:

<table>
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<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Eylea</td>
<td>4.3</td>
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<td>Aflibercept</td>
<td>414.8</td>
<td>378.1 to 451.4</td>
</tr>
</tbody>
</table>

Missing, n(%):

<table>
<thead>
<tr>
<th>Group</th>
<th>Missing, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eylea</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Clinical science
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Table 3  Descriptive statistics for responders

<table>
<thead>
<tr>
<th></th>
<th>Eylea (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central macular thickness on SD-OCT (µm), mean (SD) at 12 months</td>
<td>350.3 (93.3)</td>
</tr>
<tr>
<td>Central macular thickness on SD-OCT (µm), mean (SD) at 6 months</td>
<td>360.7 (85.2)</td>
</tr>
<tr>
<td>Change in central macular thickness on SD-OCT (µm) from Baseline to 12 months, mean (SD)</td>
<td>−139.5 (65.8)</td>
</tr>
<tr>
<td>Baseline to 6 months, mean (SD)</td>
<td>−129.1 (125.1)</td>
</tr>
<tr>
<td>ETDRS BCVA (letters), mean (SD) at 6 months</td>
<td>67.5 (10.1)</td>
</tr>
<tr>
<td>ETDRS BCVA (letters), mean (SD) at 12 months</td>
<td>68.4 (11.8)</td>
</tr>
<tr>
<td>Change in ETDRS BCVA (letters) from Baseline to 12 months, mean (SD)</td>
<td>4.7 (9.5)</td>
</tr>
<tr>
<td>Baseline to 6 months, mean (SD)</td>
<td>3.8 (6.8)</td>
</tr>
<tr>
<td>Macular volume on SD-OCT (mm³), mean (SD) at 6 months</td>
<td>8.5 (0.6)</td>
</tr>
<tr>
<td>Macular volume on SD-OCT (mm³), mean (SD) at 12 months</td>
<td>8.5 (0.8)</td>
</tr>
<tr>
<td>Change in macular volume on SD-OCT (mm³) from Baseline to 12 months, mean (SD)</td>
<td>−0.6 (0.6)</td>
</tr>
<tr>
<td>Baseline to 6 months, mean (SD)</td>
<td>−0.6 (0.6)</td>
</tr>
<tr>
<td>Retinal sensitivity (dB), mean (SD) at 6 months</td>
<td>4.93 (4.06)</td>
</tr>
<tr>
<td>Retinal sensitivity (dB), mean (SD) at 12 months</td>
<td>4.48 (3.83)</td>
</tr>
<tr>
<td>Change in retinal sensitivity (dB) from Baseline to 12 months, mean (SD)</td>
<td>−0.97 (1.92)</td>
</tr>
<tr>
<td>Baseline to 6 months, mean (SD)</td>
<td>−0.92 (2.03)</td>
</tr>
<tr>
<td>Total number of injections received over the study period (12 months), median (IQR)</td>
<td>7 (6,10)</td>
</tr>
</tbody>
</table>

Efficacy: subgroup analysis of responders only

The primary and secondary efficacy outcomes using descriptive statistics for subgroup analysis of responders within the study are provided in Table 3, figures 1–3 and supplementary information 7.

Safety: analysis of all study participants

Ocular and non-ocular AEs and serious AEs are summarised in online supplementary tables 7–9 and online supplementary information 8.

Box Plots of Change in Central Macular Thickness (responders only)

Figure 1  A graph demonstrating mean change in central macular thickness from baseline to 6 months post-baseline, and baseline to 12 months post-baseline in responders only (n=11).

DISCUSSION

This is the first prospective study to obtain safety and efficacy data over a 12-month period using serial intravitreal injections with aflibercept for the treatment of RP-CMO. There were no significant safety concerns and serial injections were well-tolerated. Eleven out of 29 (37.9%) patients were classified as responders at both 6 and 12 months having demonstrated a reduction of at least 11% CMT on SD-OCT compared with baseline. These patients experienced a mean (SD) percentage change in CMT relative to baseline of −22.9% (29.7%) and −28.1% (12.9%) at 6 and 12 months respectively. Responders gained 3.8 (SD 6.8) and 4.7 (SD 9.5) ETDRS letters respectively at 6 and 12 months. Responders demonstrated a greater change of macular volume over the study (−0.6 mm³ at 6 and 12 months) compared with non-responders (−0.3 mm³ at 6 and 12 months). When the cohort was analysed as a whole, the mean (SD) percentage change in CMT relative to baseline was −8.1% (23.3%) and −9.6% (17.6%) at 6 and 12 months respectively. An intriguing observation, unlike other disorders where anti-VEGF agents have been employed, is that all responders (n=11) achieved a notable reduction in CMO after their first injection (early-responder, Figure 2). There were no ‘late-responders’. This is clinically very valuable as for the majority of patients it may be possible to decide at a very early stage whether injections should be pursued.

Responders in this study were identified across all categories of inheritance pattern (AD, AR and XL). There was no association between response to anti-VEGF treatment and mode of inheritance. While just over half of the patients in this study had a confirmed molecular diagnosis, no specific genotype was associated with response to treatment (for example, one USH2A patient responded, two others did not; one PRPF31 patient responded, two others did not). This study included only one patient with XL inheritance who was deemed a responder and we therefore cannot draw any comparison with other patients with XL-RP. More advanced disease, defined as disruption of the ellipsoid zone within 1 mm of the fovea (seen in 27.3% of responders and 33.3% of non-responders) did not affect likelihood of response to anti-VEGF.

The release of toxic products (including VEGF) from degenerating retina/RPE in patients with RP contributes to blood-retinal barrier weakening and RP-CMO formation. Anti-VEGF is thought to act by reversing proliferation and cell migration stimulated by VEGF and the localisation of tight junction proteins induced by VEGF165. Intriguingly, Salom et al observed lower aqueous levels of VEGF in eyes of patients with RP versus controls. It would be interesting to measure levels of VEGF in the vitreous and review whether there are significant differences between patients with RP versus controls, as well as patients with RP versus those with RP-CMO. This being an invasive procedure, however, would likely prove challenging to gain ethical approval and is why we did not consider undertaking in this study.

Oxidative stress may also play a role in the development of CMO. In the case of diabetic retinopathy, raised circulating blood sugar is thought to cause dysregulation of several biochemical and molecular signalling pathways leading to the production of superoxide-free radicals and resultant oxidative stress in retinal tissues. Mitochondrial dysfunction, inflammation, and hypoxia-driven VEGF release leads to vascular and neuronal apoptosis and neovascularisation and elevated vasopermeability, respectively.

Animal models of RP have demonstrated increased production of superoxide-free radicals due to elevated oxygen levels in the outer retina. This occurs because, despite rod photoreceptor...
death and therefore reduced oxygen requirements, the choroid continues to supply the retina with the same blood flow and oxygen delivery. A study by Campochiaro et al demonstrated ocular oxidative stress in patients with RP in the absence of manifestations of systemic oxidative stress and/or damage. It is therefore possible that oxidative damage-induced cone cell death in animal models of RP may translate to human RP. Antioxidants may therefore promote cone survival and function of patients with RP. They may also influence RP-CMO.

Strengths of our study include excellent patient attendance throughout its duration, with a 96.7% participant retention rate at 12 months. The study drug was well-tolerated and no cases of endophthalmitis occurred. The study design including an initial loading phase followed by a treat and-extend regime, which allowed for the observation of both early and (potentially) late responders. We also established likely disease-causing sequence variants in 16 of 30 (53.3%) study participants.

Patients were reluctant to receive intravitreal injections without first trialling topical and/or oral treatment. A limitation to our study was therefore being unable to include treatment-naïve patients with shorter duration of CMO. All patients in the study had used topical CAI medication previously; 15 of whom were using topical CAI treatment up until 1 month prior to their screening appointment. Five of these patients were deemed responders. Five patients in the study were using oral CAI treatment up until 3 months prior to their screening appointment; one patient withdrew from the study, two patients were deemed responders, and two patients did not respond. No obvious trend was demonstrated to suggest whether recent use of topical or oral CAIs influences response to anti-VEGF therapy.

Long-standing CMO duration was observed in many patients within our cohort, with the median duration being 252 weeks (IQR, 156–296 weeks). Interestingly, duration of CMO did not appear to affect anatomical response to anti-VEGF; median CMO duration in responders was 264 weeks (IQR 228, 416), compared with the group overall (252 weeks (IQR 156, 296). In fact, the patient with the longest-standing CMO duration of the cohort (20 years) had complete resolution of CMO after a single ivA.

Our study included patients with fairly advanced underlying disease as demonstrated by photoreceptor loss and outer retinal thinning—features that have been shown to hinder VA improvement despite reduction of CMT. Indeed, three of 11 (27.3%) responders graded as having disruption of the ellipsoid zone within 1 mm of the fovea on their baseline OCT scan demonstrated no improvement of vision. Greater improvement of VA may be demonstrated in patients with a relatively more intact photoreceptor layer at baseline.

It would be valuable to repeat this study in a larger cohort of patients with molecularly confirmed genetic diagnosis,
ideally naïve to other treatment modalities, shorter history of CMO duration and relatively intact photoreceptor layer at baseline. Additional suggestions include: baseline fundus fluorescein angiogram to see whether active leakage is present and whether this predicts likelihood of response to aflibercept, baseline vitreous samples to assess VEGF levels, inclusion of a control group (possibly using placebo), randomisation of patients, to blind patients and/or clinicians and to include OCT-angiography as an additional imaging modality.

This phase II exploratory study demonstrates that ivA can be effective at reducing CMT in patients with RP-CMO, however, the factors predicting who is likely to respond remain to be clarified. There may be a role in considering intravitreal aflibercept as part of the future armamentarium when selecting treatments for patients with RP-CMO, particularly when chronic and unresponsive to alternative treatments. A larger study is required to obtain additional safety data and further investigate the role of VEGF blockade in RP-CMO.

**Contributors** SAS, TP, CB, WX, MG, SDE, AK, AW and MM: substantial contributions to the design of the work; acquisition, analysis and interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The protocol of the study adhered to the provisions of the Declaration of Helsinki and was approved by the local ethics committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. Deidentified participant data.

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**REFERENCES**


Supplementary figure 1: Consort flow diagram

Assessed for eligibility (n=295)

- Excluded (n=263)
  - Did not meet inclusion criteria (n=165)
  - Unable to contact/unresponsive (n=18)
  - Deceased (n=1)
  - Declined to participate (n=79)

Screened (n=32)

- Excluded (n=2)
  - No Cystoid Macular Edema (n=2)

Enrolled (n=30)

Allocated to intervention (n=30)

Lost to follow-up (n=1)
- Patient withdrew consent

Patients who completed study (n=29)
**Patient eligibility**

The following criteria were used to guide patient enrollment:

(A) *Inclusion criteria*: (1) patients of either gender aged ≥16 years; (2) CMO in association with RP; (3) Unilateral or Bilateral CMO (the worse eye only treated – defined as the eye with a greater central macular thickness (CMT) on OCT); (4) No previous oral treatment for CMO for last 3 months; (5) No previous peribulbar or intravitreal treatment for CMO in the study eye for last 3 months; (6) No previous topical treatment for CMO in the study eye for last 1 month; (7) Central visual impairment that in the view of the Principal Investigator (PI) was due to CMO; (8) BCVA better than 20/400.

(B) *Exclusion criteria* (ocular criteria were applied to the study eye only): (1) Insufficient patient cooperation or media clarity to allow adequate fundus imaging; (2) Evidence of visually significant vitreo-retinal traction or epiretinal membrane (ERM) on OCT that in the PI’s opinion was likely to significantly limit the efficacy of intravitreal therapy; (3) History of cataract surgery within prior 3 months or cataract surgery anticipated within 6 months of starting the study; (4) Any anti-VEGF treatment to study eye within 3 months; (5) History of YAG capsulotomy performed within 3 months; (6) Uncontrolled IOP ≥ 24 mmHg for ocular hypertension (on topical IOP lowering medications); (7) Advanced glaucoma (in the opinion of a glaucoma specialist); (8) Patients with active or suspected ocular or periocular infections; (9) Patients with active severe intraocular inflammation; (10) Patients with a new, untreated retinal tear or detachment; (11) Patients with a stage 3 or 4 macular hole; (12) Thromboembolic event (MI/CVA/Unstable Angina) within 6 months; (13) Pregnancy or family planned within 15 months; (14) Breast feeding; (15) Known allergy or hypersensitivity to anti-VEGF products.
Baseline tests of visual function

Subjective refraction and best-corrected visual acuity (BCVA)

All patients were subjectively refracted at baseline to obtain their spectacle correction. BCVA was tested monocularly at 4 metres (m) using 2 ETDRS charts (one chart for each eye) that were retro-illuminated using a light box containing 2 Cool Daylight 20 watt fluorescent tubes. If a patient was unable to read 20 letters or more at this distance, the test would be repeated at 1m. In this case, only the first 6 rows would be attempted. If the patient was wearing a trial frame, +0.75 dioptres sphere (DS) was added to the prescription to correct for the closer test distance. The VA score was the number of letters read correctly at 4m, plus the number of letters read correctly at 1m. If the patient did not require testing at 1m, i.e. they read 20 or more letters at 4m, then the score was the number of letters read correctly at 4m, plus 30.

Spectral Domain Optical Coherence Tomography (SDOCT)

The Heidelberg Spectralis SDOCT (Heidelberg Engineering, Heidelberg, Germany) was used to obtain macular volume scans in order to measure CMT. The macular volume scan protocol had the following settings: 20"x20", 49 Sections, High Speed, 29 frames automatic real time (ART).

Ishihara colour vision testing

The Ishihara version used contained 17 plates held at 75 cm from the patient. A light box was used to achieve standardised lighting and patients were adequately corrected for reading vision using plus lenses if required performing the test monocularly.

Contrast sensitivity
Contrast sensitivity was performed monocularly using the Pelli-Robson chart (Clement Clarke Inc., Columbus, OH). The patient was seated at a distance of 1m. As a standard, +0.75DS was added to each patient’s refraction when performing the test. The luminance of the chart was between 80 - 120 candela per square metre (cd/m²). The patient was asked to name each letter on the chart, starting with the high-contrast letters on the upper left-hand corner and reading horizontally across the entire line. The test was completed when the patient failed to correctly identify two or more letters in a triplet.

Retinal sensitivity

Mesopic microperimetry using the MP-1 microperimeter (Nidek Instruments, Inc, Padua, Italy) was carried out twice on each eye at baseline. Spherical error was accounted for in all patients who were then dark-adapted for 10 minutes before performing the test. The microperimetry protocol included: Cross 2 degrees, Goldmann III Stimulus 200ms, 4-2 strategy and 30 seconds of tracked fixation. The results were generated using a local defect map including -9:1 setting in order to provide mean sensitivity and mean defect together with bivariate contour ellipse area (BCEA) value (numeric and fixation).

Fundus autofluorescence (FAF)

FAF images were acquired using the Heidelberg Spectralis. For each eye, a near-infrared reflectance image and short-wavelength autofluorescence image of standard field 2 (centred on the fovea) were acquired. Both 30 and 55 degree field of view were acquired using high resolution at 50 frames (ART).
Supplementary table 1: Schedule of assessments

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*Number of total visits will vary between patients as follow-up appointments will be any time between 4 to 12 weeks.
**Intravitreal Procedure**

Aflibercept (Eylea; Regeneron, Tarrytown, New York, USA and Bayer Healthcare, Leverkusen, Germany) was supplied by Bayer LTD in vials containing 100 microlitres of 40mg/ml solution for injection, equivalent to 4mg aflibercept and stored by Moorfields Pharmaceuticals (London, UK). Each vial enabled a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept. In a designated intravitreal treatment room, under sterile conditions, using topical anesthesia and povidone-iodine 5% into the conjunctival sac and onto the lid margins, and following application of a drape and insertion of a lid speculum, injections were undertaken with a 30-gauge needle through the infratemporal quadrant, with a drop of preservative-free (PF) chloramphenicol placed in the fornix at the end of the procedure. Patency of the central retinal artery was determined by visual acuity (VA) of hand movements or better. After the injection, topical chloramphenicol was self-instilled 4 times per day for 5 days by the patients.
**Secondary outcome measures**

The secondary outcome measures relating to efficacy were: (i) The mean CMT on SDOCT at 6 months after baseline; (ii) The mean change in CMT on SDOCT from baseline to 6 months after baseline and baseline to 12 months after baseline; (iii) The mean Best Corrected Visual Acuity (BCVA) using the ETDRS visual acuity chart at a starting distance of 4m at 6 and 12 months after baseline; (iv) The mean change in ETDRS BCVA from baseline to 6 months and baseline to 12 months; (v) The mean macular volume on SDOCT at 6 and 12 months; (vi) The mean change in macular volume on SDOCT from baseline to 6 months and baseline to 12 months; (vii) Report all AEs and serious adverse events (SAEs) throughout the study; (viii) The mean retinal sensitivity using microperimetry at 6 and 12 months; (ix) The mean change in retinal sensitivity using microperimetry from baseline to 6 months and baseline to 12 months; (x) The mean number of intravitreal injections administered throughout the study.
Supplementary Information 5

Data management

The completed paper case report forms (CRFs) were checked for completion by the research nurse / research manager and data officer before data entry. All trial data were double entered by two independent data officers using the database created by the R&D IT team. The first and second data entries were compared for completion and consistency. Discrepancies were checked against the original CRF for entry errors, which were subsequently corrected. Sense checks, logic checks and range checks were also performed. Data queries were corrected and data were cleaned. The database was then locked and data transferred for data to be analysed by trial statisticians using STATA statistical software. The data management process followed Moorfields Eye Hospital standard operating procedures (SOPs) for data management.

Statistical analysis

The primary analysis was an available case analysis but baseline characteristics of those who were lost to follow up were compared with those who were not. If the findings from this study were favourable, these data would be used to plan a definitive future randomised controlled trial. Descriptive statistics have been used to report the findings of this study due to its modest sample size and single arm design. ‘Responders’ would be considered as participants demonstrating a reduction of CMT by 11% or more between baseline and 12 months, thus allowing comparison with previous studies that have used the same definition. All statistical analyses were conducted using Stata Statistical Software version 15.0.
References:


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Supplementary table 3: Non-Ocular Baseline Characteristics

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<td>Male / Female, n (%)</td>
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CME = cystoid macular edema; µm = microns; ETDRS = early treatment diabetic retinopathy study; BCVA = best corrected visual acuity; SD = standard deviation; IQR = Interquartile range; cd/m² = candela per square meter; IOP = intraocular pressure; mmHg = millimetre of mercury; SDOCT = Spectral domain optical coherence tomography; mm³ = millimetres cubed; dB = decibels
Supplementary table 5: Non-Ocular Baseline Characteristics (Responders only)

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Supplementary table 6: Ocular Baseline Characteristics (Responders only)

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</tr>
<tr>
<td>Phakic</td>
<td>10 (91)</td>
</tr>
<tr>
<td>ETDRS BCVA (letters), Mean (SD)</td>
<td>63.6 (11.3)</td>
</tr>
<tr>
<td>Ishihara colour vision (out of 17 plates), Median (IQR)</td>
<td>10 (3 to 14)</td>
</tr>
<tr>
<td>Contrast sensitivity (cd/m²), Mean (SD)</td>
<td>1.42 (0.38)</td>
</tr>
<tr>
<td>IOP (mmHg), Mean (SD)</td>
<td>12.4 (3.4)</td>
</tr>
<tr>
<td>Central macular thickness on SDOCT (µm), Mean (SD)</td>
<td>489.8 (105.9)</td>
</tr>
<tr>
<td>Macular Volume on SDOCT (mm³),Median (IQR)</td>
<td>8.9 (8.3 to 9.9)</td>
</tr>
<tr>
<td>Mean Retinal sensitivity on microperimetry (dB), Mean (SD)</td>
<td>5.8 (3.7)</td>
</tr>
</tbody>
</table>

CME = cystoid macular edema; µm = microns; ETDRS = early treatment diabetic retinopathy study; BCVA = best corrected visual acuity; SD = standard deviation; IQR = Interquartile range; cd/m² = candela per square meter; IOP = intraocular pressure; mmHg = millimetre of mercury; SDOCT = Spectral domain optical coherence tomography; mm³ = millimetres cubed; dB = decibels
**Baseline characteristics and injection frequency**

Thirty eyes of 30 patients were enrolled, with the first patient recruited in March 2016 and the final patient had their 52-week visit in August 2017. Two patients were screened who did not satisfy the criteria for enrolment (study ID 29 and 31); the reason being that they no longer had CME. The mean age of the patients was 43.3 years (SD 11.5 years, range 20 to 61 years), consisting of 17 male (56.7%) and 13 female (43.3%) patients. The study eye was the left eye in 16 (53.3%) patients and the right eye in 14 (47.7%). The median duration of CME in the study eye was 252 weeks and the interquartile range (IQR) was 156 to 296 weeks.

All patients enrolled in the study received the active drug, aflibercept. The median number of injections given across all patients in the study was 7 (IQR 6 to 9); with the minimum number of injections given being 4, and the maximum number of injections given being 11.

Likely disease-causing sequence variants were identified in 16 of 30 (53.3%) study participants (see supplementary table 2), which included: (i) AD inheritance: neural retina leucine zipper (NRL) gene (1 patient), rhodopsin (RHO) gene (2 patients), pre-mRNA processing factor 31 (PRPF31) gene (3 patients), pre-mRNA processing factor-8 (PRPF8) gene (1 patient), small nuclear ribonucleoprotein U5 subunit 200 (SNRNP200) gene (1 patient); (ii) AR inheritance: usherin 2A (USH2A) gene (3 patients), tubby like protein 1 (TULP1) gene (1 patient), retinitis pigmentosa-1 (RP1) gene (1 patient), retinol dehydrogenase-12 (RDH12) gene (1 patient), intraflagellar transport-140 (IFT140) gene (1 patient); and (iii) X-linked inheritance: retinitis pigmentosa GTPase regulator (RPGR) gene (1 patient).

The other 14 patients have undergone genetic screening (including whole genome sequencing) and remain unsolved to date.
Mean baseline ETDRS BCVA was 64 letters (SD 11.5 letters) with a mean CMT of 458.7 microns (SD 84.6 microns) in the study eye for the cohort overall. Twenty-four (80%) patients were phakic, compared with 6 (20%) patients who were pseudophakic in their study eye.

Nine of 29 (31.0%) patients were graded as having either questionable or definite presence of ERM within 3mm of the fovea. No patients were found to have vitreo-macular traction (VMT) on their baseline OCT scan. One of 29 (3.4%) patients was found to have vitreo-macular adhesion on their baseline OCT scan. Nine of 29 (31.0%) patients were graded as having either questionable or definite disruption of the ellipsoid zone within 1mm of the fovea on their baseline OCT scan.

One participant did not complete 12 months of follow-up due to illness and withdrew from the study. Since a single patient only withdrew, analysis was conducted using available case data. The baseline characteristics for this participant who withdrew from the study were not different to patients who continued in the study. Twenty-nine out of 30 (96.7%) patients therefore completed 12 months of follow-up for the study.

A post-hoc exploratory analysis of responders-only was also undertaken. Baseline characteristics for responders are summarized in supplementary tables 5 and 6. Sub-group analysis of responders demonstrated similar baseline characteristics to the group taken as a whole, with mean baseline ETDRS BCVA of 63.6 letters (SD 11.3 letters), mean CMT of 489.8 microns (SD 105.9 microns), and median duration of CME was 264 weeks (IQR 228 to 416). The median number of injections for this group was 7 (IQR 6 to 10); where the minimum number of injections given was 5, and the maximum number of injections was 11.
Supplementary figure 2

Box Plots of Change in Central Macular Thickness (all cases)

A graph demonstrating box plots of mean % change in central macular thickness from baseline to 6 and 12 months follow-up visits in the group overall (n=29).
Supplementary figure 3

Box Plots of Change in Best Corrected Visual Acuity (all cases)

Box plots of change in best corrected visual acuity demonstrating mean change from baseline to 6 and 12 months follow-up visits in the group overall (n=29).

ETDRS: early treatment diabetic retinopathy study
Efficacy: sub-group analysis of responders only

The primary and secondary efficacy outcomes using descriptive statistics for sub-group analysis of responders within the study are provided in table 3 and supplementary information 7.

Eleven out of 29 (37.9%) patients were classified as responders having demonstrated a reduction in CMT of 11% or more at 12 months compared to baseline. These same patients were also classed as responders at 6 months when applying the same criteria. Genetic mutations were identified and confirmed in 5 of 11 (45.5%) responders, which included: RPGR (1 patient), PRPF31 (1 patient), USH2A (c.11700C>A, p.Tyr3900Ter; c.4618G>A, p.Asp1540Asn) (1 patient), RHO (1 patient) and RDH12 (1 patient). The other 6 patients are genetically unsolved to date.

Following sub-analysis of these 11 patients, mean CMT at 12 months was 350.3µm (SD 93.3µm), corresponding to a change in CMT of -139.5µm (SD 65.8µm) or 28.1% (12.9 %) between baseline and 12 months. Mean macular volume at 12 months was 8.5mm³ (SD 0.8), corresponding to a change in macular volume of -0.6mm³ (SD 0.6) between baseline and 12 months. Mean CMT at 6 months was similar at 360.7µm (SD 85.2µm), corresponding to a change in CMT of -129.1µm (SD 125.1µm) or 22.9% (29.7 %) (See figure 1) between baseline and 6 months. Mean macular volume at 6 months was 8.5mm³ (SD 0.6) corresponding to a change in macular volume of -0.6mm³ (SD 0.6) between baseline and 6 months. Figure 2 demonstrates SDOCT images of 2 responders taken at baseline and at 1 month post-baseline (after having received only a single ivA).

Mean ETDRS BCVA at 6 months was 67.5 letters (SD 10.1) corresponding to a gain of 3.8 letters (SD 6.8).
Mean ETDRS BCVA at 12 months was 68.4 letters (SD 11.8) corresponding to a gain of 4.7 letters (SD 9.5) (Figure 3). It should be noted that 3 of 11 (27.3%) responders were graded as having disruption of the
ellipsoid zone within 1mm of the fovea on their baseline OCT scan. No improvement of vision was found in all 3 of these patients. Four of 11 (36.4%) responders were graded as having questionable presence of ERM within 3mm of the fovea.

Mean retinal sensitivity at 6 months was 4.93dB (SD 4.06), corresponding to a change in retinal sensitivity of -0.92dB (SD 2.03) between baseline and 6 months. Mean retinal sensitivity at 12 months was 4.48dB (SD 3.83), corresponding to a change in retinal sensitivity of -0.97dB (SD 1.92) between baseline and 12 months.

The median number of injections given in responders was 7 (IQR 6 to 10).

**Additional data of non-responders**

Eighteen out of 29 (62.1%) patients were classified as non-responders. Genetic mutations were identified and confirmed in 10 of 18 (55.6%) non-responders, which included: NRL (1 patient), RHO (1 patient), PRPF31 (1 patient), PRPF8 (1 patient), SNRNP200 (1 patient), USH2A (2 patients), TULP1 (1 patient), RP1 (1 patient) and IFT140 (1 patient). Six of 18 (33.3%) non-responders were graded as having disruption of the ellipsoid zone within 1mm of the fovea on their baseline OCT scan.
Supplementary table 7: Ocular and Non-Ocular adverse events (AEs) and serious adverse events (SAEs) – 0-6 months after baseline

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Adverse Event</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Severity</th>
<th>Relationship to Study Treatment</th>
<th>Action Taken with Study Treatment</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Floater in RE</td>
<td>11/08/2016</td>
<td>05/09/2016</td>
<td>Mild</td>
<td>Probably</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Sub-conjunctival haemorrhage</td>
<td>04/04/2016</td>
<td>05/04/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Blurring of vision</td>
<td>25/08/2016</td>
<td>06/09/2016</td>
<td>Mild</td>
<td>Possibly</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Contacted by pt to say similar blurring to 1st injection</td>
<td>07/06/2016</td>
<td>15/06/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Corneal epithelium dystrophy post injection</td>
<td>11/04/2016</td>
<td>12/04/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Back pain after bending down</td>
<td>10/10/2016</td>
<td>14/10/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Dry cornea</td>
<td>12/08/2016</td>
<td>14/08/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>LUL lesion (chalazion)</td>
<td>19/10/2016</td>
<td>06/08/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>AE ongoing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Grittiness / Dry eye</td>
<td>09/07/2016</td>
<td>16/07/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Headache post - IVT</td>
<td>26/07/2016</td>
<td>26/07/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Feeling lethargic</td>
<td>25/09/2016</td>
<td>30/11/2016</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>AE ongoing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Raised IOP post - IVT</td>
<td>03/05/2016</td>
<td>03/05/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Sub-conjunctival haemorrhage (5 days post IVT)</td>
<td>05/06/2016</td>
<td>15/06/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Trinitis</td>
<td>10/07/2016</td>
<td>06/08/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>AE ongoing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Dry ocular surface + pain</td>
<td>10/11/2016</td>
<td>16/11/2016</td>
<td>Moderate</td>
<td>Definitely</td>
<td>Discontinued permanently</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Headache</td>
<td>24/06/2016</td>
<td>26/06/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Sub-conjunctival haemorrhage</td>
<td>16/05/2016</td>
<td>19/05/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Sub-conjunctival haemorrhage</td>
<td>22/08/2016</td>
<td>26/08/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Bad back</td>
<td>15/08/2016</td>
<td>19/08/2016</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>Viral cold with headache</td>
<td>18/10/2016</td>
<td>27/10/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>Corneal abrasion</td>
<td>24/06/2016</td>
<td>25/06/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>Grittiness/Blurring using laptop</td>
<td>01/10/2016</td>
<td>18/10/2016</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>Conversion of prostate biopsy from benign to low-grade neoplasia</td>
<td>20/09/2016</td>
<td>06/12/2016</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>AE ongoing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>Vision is not as sharp</td>
<td>04/07/2016</td>
<td>06/12/2016</td>
<td>Mild</td>
<td>Possibly</td>
<td>None</td>
<td>AE ongoing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Study ID</td>
<td>Adverse Event</td>
<td>Start Date</td>
<td>Stop Date</td>
<td>Severity</td>
<td>Relationship to Study Treatment</td>
<td>Action Taken with Study Treatment</td>
<td>Outcome of AE</td>
<td>Expected</td>
<td>Serious</td>
</tr>
<tr>
<td>----------</td>
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<tr>
<td>17</td>
<td>Bad back</td>
<td>14/11/2016</td>
<td>01/01/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Yag capsulotomy (on non-study eye LE)</td>
<td>28/10/2016</td>
<td>28/10/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Feeling Low</td>
<td>01/12/2016</td>
<td>01/05/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>18</td>
<td>Viral Cold</td>
<td>22/09/2016</td>
<td>30/09/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
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<tr>
<td>19</td>
<td>Grittiness both eyes</td>
<td>12/09/2016</td>
<td>13/09/2016</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>Labyrinthitis</td>
<td>02/08/2016</td>
<td>01/04/2017</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>Sub-conjunctival haemorrhage</td>
<td>01/07/2016</td>
<td>03/07/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>Soreness of eye</td>
<td>05/10/2016</td>
<td>07/10/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
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<tr>
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<td>UTI</td>
<td>24/10/2016</td>
<td>28/10/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>Dry corneal surface</td>
<td>02/11/2016</td>
<td>03/11/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>Viral illness</td>
<td>28/12/2016</td>
<td>22/01/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>22</td>
<td>Sub-conjunctival haemorrhage</td>
<td>04/07/2016</td>
<td>09/07/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>Dry corneal surface</td>
<td>04/07/2016</td>
<td>05/07/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>22</td>
<td>Dry Eye</td>
<td>05/10/2016</td>
<td>30/10/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>23</td>
<td>Bitten by mosquito</td>
<td>10/08/2016</td>
<td>17/08/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>24</td>
<td>Flare up of mental health issues</td>
<td>15/09/2016</td>
<td>02/11/2016</td>
<td>Moderate</td>
<td>Unlikely</td>
<td>Discontinued permanently</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>25</td>
<td>Heartburn</td>
<td>31/08/2016</td>
<td>25/09/2016</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>25</td>
<td>Sub-conjunctival haemorrhage</td>
<td>08/12/2016</td>
<td>24/12/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>26</td>
<td>Viral cold (nasal congestion)</td>
<td>19/11/2016</td>
<td>24/12/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>Delayed Dose</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>27</td>
<td>Exacerbation of mental health illness</td>
<td>04/11/2016</td>
<td>17/11/2016</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>27</td>
<td>Viral illness</td>
<td>02/11/2016</td>
<td>09/11/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>27</td>
<td>Punched in non-study eye (LE) with bruise under eye</td>
<td>27/08/2016</td>
<td>31/08/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>Sub-conjunctival haemorrhage</td>
<td>05/10/2016</td>
<td>13/10/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
### Supplementary table 8: Ocular and Non-Ocular Adverse Events (AEs) and Serious Adverse Events (SAEs) – 6-12 months after baseline

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Adverse Event</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Severity</th>
<th>Relationship to Study Treatment</th>
<th>Action Taken with Study Treatment</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Perforated Ear Drum</td>
<td>26/02/2017</td>
<td>03/03/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Ear Infection</td>
<td>26/02/2017</td>
<td>03/03/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Ear Infection</td>
<td>03/04/2017</td>
<td>09/04/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Viral cold</td>
<td>03/12/2016</td>
<td>05/12/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Vision not as clear</td>
<td>15/11/2016</td>
<td>06/12/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Subconjunctival haemorrhage</td>
<td>14/12/2016</td>
<td>17/12/2016</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>Low Mood</td>
<td>20/05/2017</td>
<td></td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>AE ongoing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>Viral cold</td>
<td>13/12/2016</td>
<td>18/12/2016</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>Floater Pupil Eye</td>
<td>20/04/2017</td>
<td>27/04/2017</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>Grittiness after injection</td>
<td>06/02/2017</td>
<td>12/02/2017</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>Dry ocular surface</td>
<td>19/04/2017</td>
<td>20/04/2017</td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Viral Gastric Bug</td>
<td>09/04/2017</td>
<td>11/04/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Reduced central vision due to progression of underlying disease</td>
<td>12/05/2017</td>
<td></td>
<td>Moderate</td>
<td>Unlikely</td>
<td>Discontinued permanently</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>Posterior vitreous detachment</td>
<td>17/03/2017</td>
<td></td>
<td>Mild</td>
<td>Possibly</td>
<td>None</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>Anxiety</td>
<td>03/03/2017</td>
<td></td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>21</td>
<td>Corneal abrasion + dry cornea</td>
<td>13/01/2017</td>
<td></td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>27</td>
<td>Punched in the face just below RE (no sequelae)</td>
<td>20/03/2017</td>
<td>20/03/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>27</td>
<td>Viral illness</td>
<td>21/01/2017</td>
<td>31/01/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>Posterior vitreous detachment</td>
<td>16/02/2017</td>
<td></td>
<td>Mild</td>
<td>Possibly</td>
<td>None</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>28</td>
<td>Vitreous floater</td>
<td>05/06/2017</td>
<td></td>
<td>Mild</td>
<td>Definitely</td>
<td>None</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>30</td>
<td>Feeling low</td>
<td>17/02/2017</td>
<td>28/02/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>30</td>
<td>Right eye posterior sub-capsular cataract (non study eye)</td>
<td>17/02/2017</td>
<td></td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
### Supplementary Table 9: Ocular and Non-Ocular Adverse Events (AEs) and Serious Adverse Events (SAEs) – More than 12 months after baseline

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Adverse Event</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Severity</th>
<th>Relationship to Study Treatment</th>
<th>Action Taken with Study Treatment</th>
<th>Outcome of AE</th>
<th>Expected</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Feeling tired from fasting</td>
<td>05/06/2017</td>
<td></td>
<td>Mild</td>
<td>Not Related</td>
<td>None</td>
<td>AE ongoing</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>Vitreous Floaters</td>
<td>16/06/2017</td>
<td></td>
<td>Mild</td>
<td>Possibly</td>
<td>None</td>
<td>AE ongoing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Reduced central vision</td>
<td>25/10/2017</td>
<td>12/05/2017</td>
<td>Mild</td>
<td>Possibly</td>
<td>Discontinued permanently</td>
<td>Resolved</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>27</td>
<td>Exacerbation of mental health illness</td>
<td>17/11/2017</td>
<td>23/11/2017</td>
<td>Mild</td>
<td>Unlikely</td>
<td>None</td>
<td>Resolved</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>30</td>
<td>Viral illness</td>
<td>05/12/2017</td>
<td>12/12/2017</td>
<td>Mild</td>
<td>Not Related</td>
<td>Delayed Dose</td>
<td>Resolved</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Safety: analysis of all study participants

Ocular AEs: Ocular AEs were the expected standard range of AEs seen with intravitreal injections (see supplementary tables 7 to 9). There were no cases of endophthalmitis or retinal detachment.

Ocular SAE: One participant reported sub-acute reduction of vision at week 32 despite being a ‘responder’, with testing demonstrating a reduction in vision of 14 ETDRS letters. Injections were immediately discontinued. Further assessments were undertaken including SDOCT, FAF, microperimetry and OCT-angiography (OCT-A). There was no demonstrable change in outer retinal lamination compared to baseline, with also no change in microperimetry or FAF compared to baseline, and no abnormality detected on OCT-A. The non-study eye had a baseline vision of 30 ETDRS letters due to advanced photoreceptor loss and it was therefore concluded that the reduction in vision was most likely secondary to progression of underlying RP rather than as a consequence of ivA. The patient remained in the study and attended the 6 and 12 month follow-up appointments.

Non-ocular/systemic AEs: All non-ocular/systemic AEs were reported during the study whether or not they were considered to be secondary to aflibercept. Non-ocular/systemic AEs included: back pain, headache, lethargy, tinnitus, viral cold, conversion of prostate biopsy from benign to low-grade neoplasia, feeling low/low mood, labyrinthitis, urine tract infection, relapse of mental illness, heartburn, perforated ear drum, ear infection, viral gastric illness, anxiety and mosquito bite.

Whilst the participant who developed labyrinthitis during the study was reassured that it was unlikely to be secondary to aflibercept, they decided that they would prefer to discontinue receiving injections. This patient remained in the study and attended the 6 and 12 month follow-up appointments.