DOI:
10.1016/S0140-6736(17)31193-5

Document Version
Peer reviewed version

Clinical Efficacy of intravitreal aflibercept versus panretinal photocoagulation on best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded randomised, controlled phase IIb non-inferiority trial.

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Research in context

Evidence before this study

Panretinal laser photocoagulation (PRP) is the standard of care for patients with proliferative diabetic retinopathy (PDR). Currently, 3 anti-vascular endothelial growth factor (anti-VEGF) therapeutic agents are administered by intravitreal injections to treat ophthalmic conditions. Bevacizumab and ranibizumab are monoclonal antibodies against VEGF A. Pre-CLARITY trial, we reviewed PubMed articles between January 1st 2005 and January 31st 2014 and there were 8 short-term randomised controlled trials (RCTs) comparing either bevacizumab or ranibizumab monotherapy or in combination with PRP versus PRP alone in high risk PDR. These RCTs showed new vessel regression with these agents after 3 to 4 months.
Aflibercept is the latest anti-VEGF agent and it blocks all isomers of VEGF A, B, placental growth factor 1 and 2, and galectin-1. To date, there have been no RCTs on aflibercept in PDR.
We updated the review on March 1st 2017. A well-designed multicentre clinical trial comparing ranibizumab monotherapy versus PRP in patients with high risk PDR, with and without macular oedema, has been published. Primary outcome of this RCT at 2 years showed non-inferiority of ranibizumab versus PRP in high risk PDR with a median of 10 injections over 2 years (7 injections in the first year). However, this RCT has not changed clinical practice worldwide due to the perceived difficulties with practicalities of delivering repeated intravitreal injections in PDR patients and the study only showed non-inferiority of BCVA to PRP albeit beneficial secondary outcomes. Therefore, PRP remains the preferred choice.
In addition, a substantial proportion of patients after initial PRP are under long-term follow-up in retinal clinics to identify and treat reactivation of existing neovascularisation with supplemental PRP and these patients have been excluded from previous clinical trials. Therefore, the role of anti-VEGF in this patient cohort remains unclear.

Added value of this study

The CLARITY study is the first RCT on intravitreal aflibercept in PDR and it provides substantial evidence that the visual outcome of active PDR at one year with aflibercept therapy is superior to PRP. This is also the first study to show a superior visual acuity outcome with an anti-VEGF agent in eyes with PDR with no baseline macular oedema. Furthermore this effect was achieved with 4 aflibercept injections (a median of 1 injection after the 3 loading doses in a year) irrespective of the PDR risk status and previous PRP treatment history, providing important evidence that aflibercept therapy can be adopted as an alternative to PRP in the first year of therapy. The study also showed a significantly lower incidence of macular oedema and vitreous haemorrhage and fewer adverse effects on binocular visual acuity and visual fields with aflibercept compared to PRP further highlighting the advantages of aflibercept over PRP with comparable systemic adverse effects. Most importantly, the patient satisfaction scores suggest patient preference for aflibercept therapy over PRP in a clinical trial setting.

Interpretation

In the first year of therapy, aflibercept is an effective treatment for active PDR and may be adopted as an alternative option to PRP.

Abstract

Background: Proliferative diabetic retinopathy (PDR) is the most common cause of severe sight impairment in diabetes mellitus. PDR has been managed by pan-retinal laser photocoagulation (PRP) for the past 40 years. Here we report the 1-year safety and efficacy of intravitreal aflibercept.

Methods:
Adults with treatment naïve or post-laser treated active PDR from 22 UK ophthalmic centres were recruited to this phase 2b, non-inferiority trial and randomly assigned (1:1) to repeated intravitreal aflibercept or PRP standard care for 52 weeks. Randomisation was by minimization using a web-based computer generated system. Primary outcome assessors were masked optometrists. The treating ophthalmologists and participants were not masked. The primary outcome was defined as a change in best-corrected visual acuity (BCVA) at 52 weeks using a linear mixed-effects model that estimated adjusted treatment effects at both 12 and 52 weeks, having excluded fluctuations in BCVA owing to vitreous haemorrhage. This modified intention-to-treat analysis was re-applied to the per protocol participants. The non-inferiority margin was pre-specified as -5 letters. Safety was assessed in all participants. Trial registration: ISRCTN32207582.

Findings.
We recruited 232 participants (116 per arm) between August 2014 and November 2015. 221 participants (n=112 aflibercept arm, n=109 PRP arm) contributed to the modified intention-to-treat model, and 210 participants (n=104 aflibercept arm and n=106 PRP arm) within per protocol. Aflibercept was non-inferior and superior to PRP in both the modified intention-to-treat population (mean BCVA difference 3.9 letters; 95% CI 2.3-5.6 letters; p<0.0001) and the per protocol population (difference 4.0 letters; 95% CI 2.4 -5.7 letters, p<0.0001). There were no safety concerns.

Interpretation.
Intravitreal aflibercept in PDR results in improved outcome at 1 year compared to PRP standard care.

Funding
The Efficacy and Mechanism Evaluation Programme, a Medical Research Council and National Institute for Health Research partnership; Aflibercept was supplied by Bayer Plc, Reading, UK.

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Introduction

Proliferative diabetic retinopathy (PDR) is the commonest cause of severe visual loss in people with diabetes.[1] It is characterised by the growth of new abnormal vessels on the retina or optic disc that can result in sight threatening complications such as vitreous haemorrhage and tractional retinal detachment.

Panretinal laser photocoagulation (PRP) has been the standard of care for this condition for over 40 years and reduces the risk of severe visual loss by 50%. [2] Patients identified with active PDR are treated urgently to complete initial PRP and then reviewed regularly to identify and treat recurrent or de novo active neovascularisation with supplemental PRP. Repeated supplemental PRP is associated with permanent sequelae on visual function including final visual acuity below the driving standard, restricted visual fields that preclude driving, night vision difficulties, loss of colour vision and reduced contrast sensitivity and increased macular oedema.[3-7] Although laser technology and techniques have evolved over the last decade to reduce side-effects, [5, 6] approximately 4.5% progress to require vitrectomy surgery.[8] Therefore, there is a significant unmet need for novel treatments that reduce the risk of severe visual loss in PDR non-inferiority PRP with fewer side-effects.

Ranibizumab and bevacizumab, monoclonal antibody inhibitors of vascular endothelial growth factor-A (VEGF-A), have been shown to cause short-term new vessel regression, either as monotherapy or in combination with PRP. [9] Since this study commenced, a randomised clinical trial comparing ranibizumab and PRP reported 2-year outcomes in high risk PDR with and without macular oedema and showed ranibizumab monotherapy is non-inferior to PRP, with less visual field loss and incident vitrectomy. [10] The latest anti-VEGF agent, aflibercept (Bayer Pharma AG, Berlin, Germany), is a recombinant fusion protein comprising the binding domains of VEGF-1 and -2 receptors, binds to VEGF with greater affinity than ranibizumab or bevacizumab and demonstrates activity against VEGF-A, -B, and placental growth factor. [11] This is the first study to evaluate efficacy and safety of intravitreal aflibercept in the management of PDR.

Methods

Study design and participants

CLARITY is a multicentre, prospective, two-arm, parallel-group, randomised, non-inferiority trial. Patients were recruited from 22 UK National Health Service hospitals.

The study was granted approval by the National Research Ethics Committee Service London - South East (14/LO/0203). Clinical Trials Authorisation was given by the MHRA (11518/0013/001-0001) and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) number was 2013-003272-12. Trial Steering and Data Monitoring Committees provided independent oversight.

Eligible patients with type 1 or 2 diabetes mellitus, aged 18 years or older, with clinical evidence of treatment naïve PDR or persistent retinal neovascularization following initial PRP requiring additional PRP (i.e. non treatment naïve) were included. Best corrected visual acuity (BCVA) was ≥54 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, equivalent to 6/24 Snellen BCVA with sufficient media clarity and pupillary dilatation for adequate fundus photographs. The fellow eye Snellen BCVA was ≥ 2/60. Women patients were using effective contraception, post-menopausal for ≥ 12 months prior to trial entry, or surgically sterile. Study eye exclusion criteria were co-existent ocular disease that affected or may affect visual acuity or prevent treatment delivery. As diabetic macular oedema can co-exist with PDR and confound visual acuity outcomes, all eyes with clinical evidence of diabetic macular oedema and spectral domain optical coherence tomography central subfield thickness ≥ 300µm due to macular oedema were excluded. Other ocular exclusions were moderate or dense vitreous haemorrhage preventing clear visualisation of the macula and/or optic disc or preventing laser treatment, fibrovascular proliferation or tractional retinal detachment in the posterior pole, prior vitrectomy, other causes of retinal neovascularization, and anticipated need for cataract extraction or vitrectomy within 12 months. Patients treated with intravitreal anti-VEGF or steroid for DMO within 4 months or PRP within 8 weeks prior to screening were excluded. Systemic exclusion criteria included haemoglobin A1c (HbA1c) ≥12%, blood pressure ≥170/110 mmHg and any medical condition that, in the opinion of the investigator, precluded participation in the study. The clinical assessments schedule is detailed in **table S1 and S2, appendix** and in the published protocol.[12]

Randomisation and masking

Patients provided informed consent and those eligible were randomly allocated (1:1) to either repeated intravitreal aflibercept 2mg/0.05ml (Bayer Pharma AG) or PRP using the method of minimisation, concealed before allocation, stratified by site, baseline PDR status (naïve versus non-naïve), BCVA (54-69 versus ≥70 ETDRS letters), HbA1c (<8% [<63.89mmol/l], ≥8% to ≤10% [63.90 to 85.8mmol/mol] and >10% [>85.81mmol/mol], diastolic blood pressure (≤90mmHg versus >90mmHg) by collaborating site investigators via the King's Clinical Trials Unit web-based randomisation service. Patients and clinical investigators were unmasked due to the anatomical changes induced by the comparator. Outcome assessors including optometrists, visual field technicians, imaging technicians and the Independent Reading Centre were masked to treatment allocation. Primary outcome assessors completed a treatment guess form to determine masking success.

Procedures

The intervention arm received intravitreal aflibercept injections (Bayer Pharma AG). The dose of each intravitreal aflibercept injection was 2 mg/0.05ml and patients received mandated injections at baseline, 4 and 8 weeks. From week 12, patients were reviewed every four weeks and aflibercept injections were given *pro-re-nata* based on the degree of regression and reactivation of neovascularisation of disc and elsewhere observed on clinical examination with adequate visualisation of entire retina and compared to 7-field colour photographs or wide-field photography at screening or previous visit. Patients were categorised into 3 groups according to treatment response into no regression, partial regression and total regression as shown in **table S3, appendix**. Treatment was deferred at the investigator's discretion where eyes had

experienced adverse events such as vitreous haemorrhage, retinal detachment or raised intraocular pressure >30mmHg. If aflibercept became contraindicated during the trial (e.g. newly pregnant woman), patients were treated with PRP. The comparator arm received standard PRP treatment delivered as per routine clinical practice by direct, single or multispot or indirect means targeting areas of non-perfusion initially. Patients in the PRP arm had PRP at baseline and in fractionated fortnightly sessions thereafter, with follow-up at week 12. From week 12, PRP arm patients were assessed for treatment response every 8 weeks and regression patterns categorised exactly as the aflibercept arm. Treatment in the PRP arm was deferred if the media was too hazy or if the investigator judged that the eye had receive adequate PRP.

BCVA was measured at 4 metres using validated ETDRS visual acuity charts employing standard operating procedures for studies in diabetic retinopathy. Refracted visual acuity was done at screening, 12 and 52 weeks and withdrawal. Secondary outcomes included Pelli Robson contrast sensitivity letter scores, uniocular and binocular percentages Esterman driving visual field efficiency score (missed spots), colour fundus photography, OCT and fundus fluorescein angiography. Patient related outcomes were measured using validated questionnaires at screening and 52 weeks. These included National Eye Institute -Vision-Related Quality of Life (NEI-VFQ 25), a diabetic retinopathy specific quality of life questionnaire (RetDQoL) and diabetic retinopathy treatment satisfaction questionnaire (RetTSQ). Health-related quality of life, activity scales and health and social care service use will be reported in a subsequent cost-effectiveness paper. A subset of patients (n=40) also underwent oximetry and this mechanistic component of the study will be reported later.

Outcomes

The primary outcome was BCVA letter change from baseline to 52 weeks in study eye in the aflibercept arm relative to the PRP arm. A secondary outcome was BCVA change from baseline to 12 weeks. Additional secondary visual function outcomes assessed at 52 weeks included uniocular and binocular Esterman missed spots, binocular visual acuity letter scores, low luminance visual acuity letter scores, categories of visual acuity outcomes in terms of visual gain or loss, and contrast sensitivity letter scores. Change from baseline between arms in patient reported outcomes using NEI-VFQ-25, RetDQol, RetTSQ at 52 weeks. Anatomical outcomes included new vessel regression patterns and change in ETDRS diabetic retinopathy severity score levels at 12 and 52 weeks (**table S4, appendix**). [13] The number of treatments required in both arms and the proportion of patients requiring supplemental PRP in the aflibercept arm were reported. We evaluated differences in ocular and systemic safety profile between arms from baseline to 52 weeks.

Adverse events were recorded per visit, site investigators determined relatedness and Chief Investigator determined expectedness of all serious adverse events. Adverse events were coded by two masked clinicians.

Statistical analysis

The intention-to-treat population was defined to comprise all randomised patients. The per protocol population was defined to exclude those randomised patients found to be ineligible at entry, and those not receiving the full randomised treatment up to and including the 8-week visit (whether due to discontinuation, exclusion or other

reason for missing a randomised treatment in this period). A statistical analysis plan was finalised before data lock and agreed with oversight committees. The primary outcome of refracted BCVA was compared between arms primarily at the 52-week point and secondarily at the 12-week point using a linear mixed effects model with patient as a random effect to allow for within-patient correlation of repeated measures over time. Fixed effects included the main effects and interactions with "time" (12 and 52 weeks) for treatment arm, the minimisation stratifiers: PDR status, contrasts for HbA1c, blood pressure, the baseline of the outcome and its missing indicator required for the missing indicator method. [14]As pre-specified, any BCVA measurement at 12 and 52 weeks which was both >3SD below the mean at that time point (including all measurements) and recorded within 3 months of the occurrence of a vitreous haemorrhage was excluded from analysis to avoid erroneous influence on the statistical analysis. Some sites recruited a very small number of patients and so study site was not included in models to allow these patients to contribute to estimating treatment effects rather than site effects. The test for non-inferiority was one-sided at the 2.5% significance level, and is presented as an estimated effect with two-sided 95% confidence interval compared against the non-inferiority margin of -5 letters. For the analysis of the primary outcome, the mixed effects model was re-fitted within the per protocol population. Analyses were completed according to the intention-to-treat strategy with intention-to-treat and per protocol analyses modified for missing and excluded data together with principled sensitivity analysis in the full intention-to-treat and per protocol populations.[15, 16] Secondary continuous outcomes were analysed only on the intention-to-treat basis modified for omitted data and with the same model specification as for the primary outcome, and reported as adjusted differences in means. All tests were two-sided at the 5% significance level and effect sizes interpreted cautiously with 95% confidence intervals. Safety and other categorical outcomes are reported as proportions with 95% confidence intervals and Pearson's chi-squared tests, or Fisher's exact tests and Wilson's exact confidence intervals when any expected table counts were smaller than five.

Sensitivity to the missing at random assumption made in the primary outcome analysis was undertaken in all randomised patients to assess sensitivity to the handling of missing and excluded 52-week data, using three recommended scenarios affecting either one or both arms.[16] Sensitivity analysis was used to assess the use of concomitant treatments, to assess changes to conclusions from inclusion of isolated outliers in statistical analyses defined as exceeding four standard deviations from expected, and to assess additional adjustment for all sites as a fixed effect.

Pre-planned subgroup analyses for primary outcomes were done by extending the models to include interaction terms with arm for the randomisation stratifiers including baseline visual acuity, HbA1c, diastolic BP and PDR status (naïve and non-naïve).

The planned sample size was 220 participants. Detailed sample size calculations are available in the published protocol. The SD of the change in visual acuity, after adjustment for baseline, was anticipated to be 10.3, based on the estimate from a relevant trial.[17] In brief, the study had at least 90% power to detect non-inferiority of -5 letters using a two-sided 95% confidence interval from an analysis of covariance test with adjustment for baseline visual acuity.[12, 16]

Role of the funding source

Neither the funders nor the provider of active medication had any role in study design, patient recruitment, data collection, data analysis, data interpretation, writing or editing the report or the decision to submit for publication. The statisticians had full access to all data in CLARITY and the Chief Investigator had final responsibility for the decision to submit for publication.

Results

Between August, 2014, and December, 2015, 290 patients were assessed for eligibility and 232 randomly assigned to receive intravitreal aflibercept (n=116) or PRP (n=116) (**figure 1**).

Baseline characteristics were well balanced between treatment groups (**table 1**). A total of 123 (53%) treatment naïve and 109 (47%) non-naïve patients were recruited. Mean baseline BCVA was 81·4 (SD 8·1) ETDRS letters. The proportion of patients with baseline BCVA 54-69 and ≥70 ETDRS letters were 9% and 91% respectively.

Derivation of the Intention- to-treat model and Per-protocol populations

Patients included in the pre-specified Intention-to-Treat linear mixed effect model were derived as follows: (1) The BCVA data were available for 211 patients of 232 randomly assigned patients (107 in aflibercept and 104 in PRP arms) at 52 weeks and for 214 patients at 12-weeks (109 in aflibercept and 105 in PRP arm); (2) A total of 4 patients in the PRP arm at 12 weeks and 2 patients in the aflibercept arm at 52 weeks were excluded due to presence of vitreous haemorrhage within 3 months of BCVA recordings and BCVA was more than 3SD below the mean at that time point (including all measurements); (3) There were 198 patients with BCVA available at both 12 and 52 weeks. A total of 11 patients had BCVA recorded at 52 weeks and not 12 weeks (8 in PRP arm and 3 in aflibercept arm). In addition, there were 12 patients who had BCVA recorded at 12 weeks but not at 52 weeks (5 in PRP and 7 in aflibercept arm); (4) Therefore, there were 221 patients that contributed to the analysis in the linear mixed effect model for the intention-to-treat strategy (109 in the PRP arm and 112 in the aflibercept arm); (5) A total of 18 patients did not meet the PP definition and were not included in the PP population (n=214). This included 11 (9·5%) patients in the aflibercept arm and 7 (6·0%) in the PRP arm), with 4 patients in the aflibercept arm and 4 in the PRP arm not being compliant with the eligibility criteria and a further 7 patients in the aflibercept arm and 3 in the PRP who did not receive initial mandatory treatment requirements. Therefore, there were 210 patients that contributed to the PP analysis in the LME model (106 in the PRP arm and104 in the aflibercept arm).

Primary outcome

Primary outcome at 52 weeks showed aflibercept was superior to PRP in terms of BCVA in both intention-to-treat and per-protocol populations (**table 2**). Adjusted difference between arms fell above the pre-specified acceptable margin of -5 letters for the 95% CI at both 12 and 52 weeks.

Three sensitivity analyses on the population with completed follow-up at 52 weeks were done, adjusting for sites, outliers and missing data. No patients were offered anti-VEGF treatment for macular oedema in the PRP arm. So sensitivity analysis for concomitant treatments was not required. When sites were considered, the adjusted difference in BCVA between arms remained significant at 4·1 letters (95% CI 2·4 to 5·7), $p<0·0001$, and 4·1 letters (95% CI 2·4 to 5·7), $p<0·0001$, respectively in the

modified intention-to-treat and per protocol populations. A total of 207 and 198 patients remained after outliers in the modified intention-to-treat and per protocol populations, defined as less than or more than 4SD were removed. This sensitivity analysis showed the adjusted difference in BCVA between arms as significant at 4·0 letters (95% CI 2·7 to 5·4, $p<0·0001$) in the modified intention-to-treat and 4·1 letters (95% CI 2·7 to 5·5, $p<0·0001$) in the per protocol population. The sensitivity analysis for missing data also confirmed a superiority effect in both intention-to-treat (n=232) and per protocol populations (n=214) for three pre-specified alternative scenarios (**figure 2, appendix**).

Primary outcomes in treatment naïve and non-naïve groups are shown in **table S5.**

Secondary outcomes

Table S6 shows visual acuity in each stratum of visual acuity ranges at 52 weeks.

The proportion of patients with greater or equal to 10 letter improvement and able to do so with baseline BCVA ≤90 was 5% (5/101) in the aflibercept arm compared to 2% (2/95) in the PRP arm (difference between arms was 2·8% (95% CI -3.1% to 9.1%, $p=0·45$). The proportion of patients with greater or equal to 10 letter worsening was 5% (5/107) in the aflibercept arm compared to 15% (16/104) in the PRP arm (difference between arms was 10·7%, 95% CI 2·6% to 19·3%, $p=0·009$). There were 5% (5/107) of patients with greater or equal to 15 letter worsening in the aflibercept arm and 6% (6/104) in the laser arm (difference between arms was 1·1%, 95% CI (-5.5% to 7.9%), p=0·72).

Binocular Esterman scores showed significant worsening with the PRP arm. This was also reflected in lower binocular visual acuity scores in the PRP arm (**Table S7**). Other visual function tests did not vary between arms**. Table S8** shows changes in visual function in treatment naïve and non-naïve cohorts.

The RetDQoL scores (**table S9**) and NEI-VFQ scores (**table S10**) did not show significant differences between arms. RetTSQ scores showed that patient satisfaction scores were significantly better in the aflibercept arm and the adjusted mean difference was 3·0 (95% CI 0·4 to 5·5, p=0·022) (**table S9**).

Anatomical outcomes

Macular thickness and volume significantly increased in the PRP arm compared to the aflibercept arm **(table S11**). The proportion of patients with new onset centre-involving macular oedema also increased significantly in the PRP arm **(table S12).**

Treating investigators determined regression and reactivation patterns of retinal new vessels to decide re-treatment based on pre-defined criteria. **Table S13** shows that a significant proportion of eyes showed total regression of retinal new vessels in the aflibercept arm compared to the PRP arm. The difference in proportions of total regression favouring the aflibercept arm was 30% (95% CI 16% to 42%), $p<0·0001$ at 52 weeks.

The UK Network of Reading Centres (Networc UK), masked to treatment allocation, graded ETDRS diabetic retinopathy severity scores from colour fundus photographs obtained at baseline, 12 and 52 weeks.[13] Of patients with gradable photographs

(n=227), 175 (77%) were graded low risk PDR (Levels 61 and 65) and 52 (23%) high risk PDR (Levels 71 and 75). Three eyes were graded below level 61 (**table S14**). Improvement from diabetic retinopathy severity score is difficult to assess in lasered eyes and so the improvement of the level of remaining retinopathy was graded. Change in diabetic retinopathy severity level in treatment naïve eyes treated with aflibercept is also reported in **table S15**. A significantly higher proportion of patients in the PRP arm remained at PDR (level 61 or above) compared to the aflibercept arm at both 12 and 52 weeks.

Treatment outcomes

The proportion of patients that received treatment according to protocol was 94% (109/116) in the aflibercept arm and 97% (113/116) in the PRP arm. The treatment allocation guess form, measuring success of masking of primary assessors to treatment allocation, was reported for 210 participants. Assessors guessed correctly for 15% (32/210), incorrectly for 10% (20/210), and were unable to tell for 75% (158/210) of participants.

By 52 weeks, aflibercept arm patients received a mean (SD) of 4·4 (1·7) injections, (95% CI 4·1 to 4·7), [Median (IQR) 4.0 (3.0 to 5.0)] including the 3 mandated loading doses. The mean number of aflibercept injections in treatment naïve patients was 4·6 (1·6) [Median (IQR) 4 (3, 6)] while non-naïve patients received a mean number of injections 4·1 (1·8), [Median (IQR) 4·0 (3·0 to 4·8)]. A total of 2 (1·6%) patients required supplemental PRP in the aflibercept arm.

In the PRP arm, 78 (69%) received multispot laser and the remaining received single spot laser. The type of laser delivery was not recorded for 3 patients. Distribution of PRP session numbers required were 1 session in 35 eyes (30·2%); 2 sessions in 25 eyes (21·6%), 3 sessions in 10 eyes (8·6%), 4 sessions in 4 eyes (3·4%) and 5 sessions in 1 eye (0·9%). From week 12, 75 patients (65%) in the PRP arm required supplemental PRP. The mean number (SD) of supplemental PRP sessions required was 1·17 (1·16), 95% CI (0·96 to 1·38) with the treatment naïve patients requiring 1·35 (1·28) sessions and in the non-naïve arm, the mean was 0·96 (0·96).

Safety outcomes

When comparing other complications of PDR between arms, incidence of vitreous haemorrhage was higher in the PRP arm (p=0.034). The proportion of patients requiring vitrectomy was small and not significant between arms (p=0·066). There were no cases of endophthalmitis in the study eye (**table 3**).

Ocular adverse events in the non-study eye are shown in **table S16.** The number of vitreous haemorrhages in the non-study eye was recorded, as this complication may confound both the vision–related and health-related quality of life assessments. The Anti-Platelet Trialists` Collaboration (APTC) defined events showed no significant difference between arms (**table 4**). [18] Frequency of systemic adverse events did not differ between treatment arms (**table S17**).

Discussion

The results of this phase IIb trial demonstrate that intravitreal aflibercept monotherapy is superior to standard PRP treatment for PDR through 52 weeks. This is the first study to show that an anti-VEGF therapy can provide superior BCVA outcomes in

eyes with active PDR without baseline centre-involving macular oedema. Mean difference in BCVA letter score between arms in favour of aflibercept was small but significant, and was achieved with a median of one aflibercept injection only in the 40 weeks post loading phase, indicating that aflibercept is a feasible new approach for compliant patients.

Superior treatment satisfaction scores in the aflibercept arm were unexpected but highlighted patients' preference for this therapy. The lower incidence of centre-involving macular oedema and vitreous haemorrhage observed in the aflibercept arm may have contributed to both the mean BCVA improvement and patient preference as these conditions are the most common causes of symptomatic visual impairment in patients with PDR. The proportion of patients with no macular oedema at 52 weeks was 89% (93/105) in the aflibercept arm compared to 71% (74/104) in the PRP arm. The incidence of vitreous haemorrhage was twice as high in the PRP arm (18% (21/116) compared to 9% (10/116) in the aflibercept arm).

Other factors that may explain the superior effect of aflibercept may include a high aflibercept VEGF binding affinity and blockade of other angiogenic pathways such as placental growth factor and galectin-1.[19, 20] However, the exact mechanisms of these pathways in PDR remain to be understood.

The superior BCVA findings were supported by significantly better binocular visual acuity and binocular Esterman scores in the aflibercept arm. These observations have significant impact on eligibility to retain a driving licence. In the UK, the Driver and Vehicle Licensing Agency (DVLA) have designated both a minimum visual acuity and Esterman visual field standard to maintain a valid driving licence. [21] With advances in laser technology and techniques, there are reports with short follow-up suggesting that modern-day laser techniques and technology such as multispot laser have reduced the prevalence of visual field loss with PRP.[6, 21, 22] However, our study shows that despite 69% of the study cohort being treated with multispot laser, aflibercept is associated with lower risk of visual field loss than modern day laser at 52 weeks, in keeping with findings noted in the recent ranibizumab trial in PDR at 2 years.[10]

Other visual outcomes that measured adverse effects of PRP such as contrast sensitivity and low luminance visual acuity were not significantly different between arms, although removing outliers suggested greater preservation of low luminance visual acuity letter score by 52 weeks in the aflibercept arm.

Despite the good visual outcomes observed with this intervention with a median of only 4 injections in the first year, the acceptance rate amongst clinicians may vary because PRP is perceived to have a permanent effect and require fewer follow-up visits than anti-VEGF therapy. However, our study demonstrates that 65% of the patients in the PRP arm required supplemental PRP when monitored every 8 weeks over 52 weeks. The ranibizumab study also reported that 45% of the patients in the PRP arm required additional sessions by the end of two years.[10] More importantly, loss of visual acuity of 10 or more letters was five times more common with PRP than aflibercept.

The disease modifying effect of aflibercept is well established from diabetic macular

oedema trials, where aflibercept improves the level of diabetic retinopathy severity, alongside its effect on diabetic macular oedema.[23] This anatomical effect should also be considered when choosing between anti-VEGF and PRP as a first line option in PDR. As aflibercept is licensed for diabetic macular oedema, the findings of this study indicate that aflibercept is also effective in the management of PDR in the first year, allowing the use of a single agent to address both of these sight-threatening complications of diabetes.

The robust RCT design, high statistical power and excellent retention rates are particular strengths of this study. The study patients are representative of PDR population, therefore these findings can be generalised to clinical practice for the first year of therapy. Re-treatment criteria used in CLARITY are very similar to those followed in the ranibizumab trial[10] and determined by treating investigators at each study visit. Compliance with treatment (94% aflibercept arm and 97% PRP arm) was very good in CLARITY, indicating that these re-treatment criteria can be easily applied to routine clinical practice.

The safety evaluation of aflibercept in CLARITY revealed no new concerns. There were no differences in APTC events or other systemic adverse events between arms.

The limitation of this study is that it was a Phase IIb study with follow-up for only 52 weeks. To date, the only other well-designed study on anti-VEGF for PDR included patients with diabetic macular oedema and so the treatment regimen was pre-planned to be more intense than this study.[10] However, as a 5 year study, it will provide long-term outcomes of ranibizumab in PDR, information on the disease modifying effect of anti-VEGF and the long-term compliance of patients.

In conclusion, this is the second study to show non-inferiority of anti-VEGF to PRP and the first study to show potential advantage in BCVA versus PRP with an anti-VEGF agent, in this case aflibercept. The study also shows that patients prefer anti-VEGF to PRP in a clinical trial setting. However, longer-term studies are required to evaluate long-term patient compliance and the disease modifying effect of different anti-VEGF agents in PDR both in Phase 3 clinical trials and in real-life setting.

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Acknowledgment

The CLARITY study group thanks all the patients who participated in the study, and the many individuals not specifically mentioned in the paper who have supported the study. We would also like to thank Gill Lambert, Beverley White-Alao, Oliver Pressey, Negin Sarafraz-Shekary, Evangelos Georgiou, Janice Jimenez and team at King's College Clinical Trials Unit. We would also like to that the Royal Free London NHS Foundation Trust Pharmacists and members of the independent UK Network of Ophthalmic Reading Centres (Networc UK) for their support of the trial. We would like to thank the Lay Panel in the North East Diabetes Research Network and Mr Richard Lane OBE, lay representative grant co-applicant.

This investigator initiated study was funded by EME (12/66/15) and managed by NIHR on behalf of the MRC-NIHR partnership; Drug (aflibercept solution for injection) was supplied by Bayer Plc, Reading UK. We thank the NIHR Clinical Research Network. The research was supported by the NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, the NIHR Moorfields Clinical Research Facility and the UKCRC-registered King's Clinical Trials Unit at King's Health Partners which is part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley, NHS Foundation Trust and King's College London. We would also like to thank Maggie Shergill, the Research Manager (Monitoring) and the other team members of the NIHR Evaluation Trials and Studies Coordinating Centre (NETSCC). This report presents independent research supported by the NIHR. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Author Contribution

The study was conceived by the Chief Investigator (SS) and co-lead (PH). The study was designed by the grant co-applicants (SS, PH, AP; JK; CM; RTE; JB; PH; DH). King's Clinical Trial Unit core team: AR, JK, CM; AR: Trial Manager. AP and JV provided the statistical input. SS drafted the manuscript and all authors commented on drafts and approved the final version.
Collaborators listed acted as coordinators of the trial at each clinical site and recruited and managed patients (AB, BB, UC, HE, TE, RG, SG, MH, SK, AL, MM, LM, GM, BM, LN, OO, JP, PP, RP, JR, AR, AS, JT); leads of UK Reading Centre (UC, TP,

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Data monitoring committee

Professor Sarah Walker (Oxford University, Oxford, UK; Chairman), Miss Evelyn Mensah (Central Middlesex NHS Trust, UK), Mr. Niral Karia (Southend NHS Trust).

Drug supply

Aflibercept was provided by Bayer Plc, Reading, UK in accordance with its marketing authorisation. The Clinical Trials Manufacturing and Supplies Department, Pharmacy Production Department, Royal Free Hospital NHS Foundation Trust, was responsible for packaging, labelling and QP releasing the drug prior to distribution to site.

Conflicts of interest

SS has received research grants, travel grants, speaker fees and attended advisory board members of Novartis, Bayer, Allergan and Roche. PH has received research grants, travel grants, speaker fees and attended advisory board members of Novartis, Bayer, Allergan. The other named authors declare that they have no competing interests.

Figure 1: Trial Profile

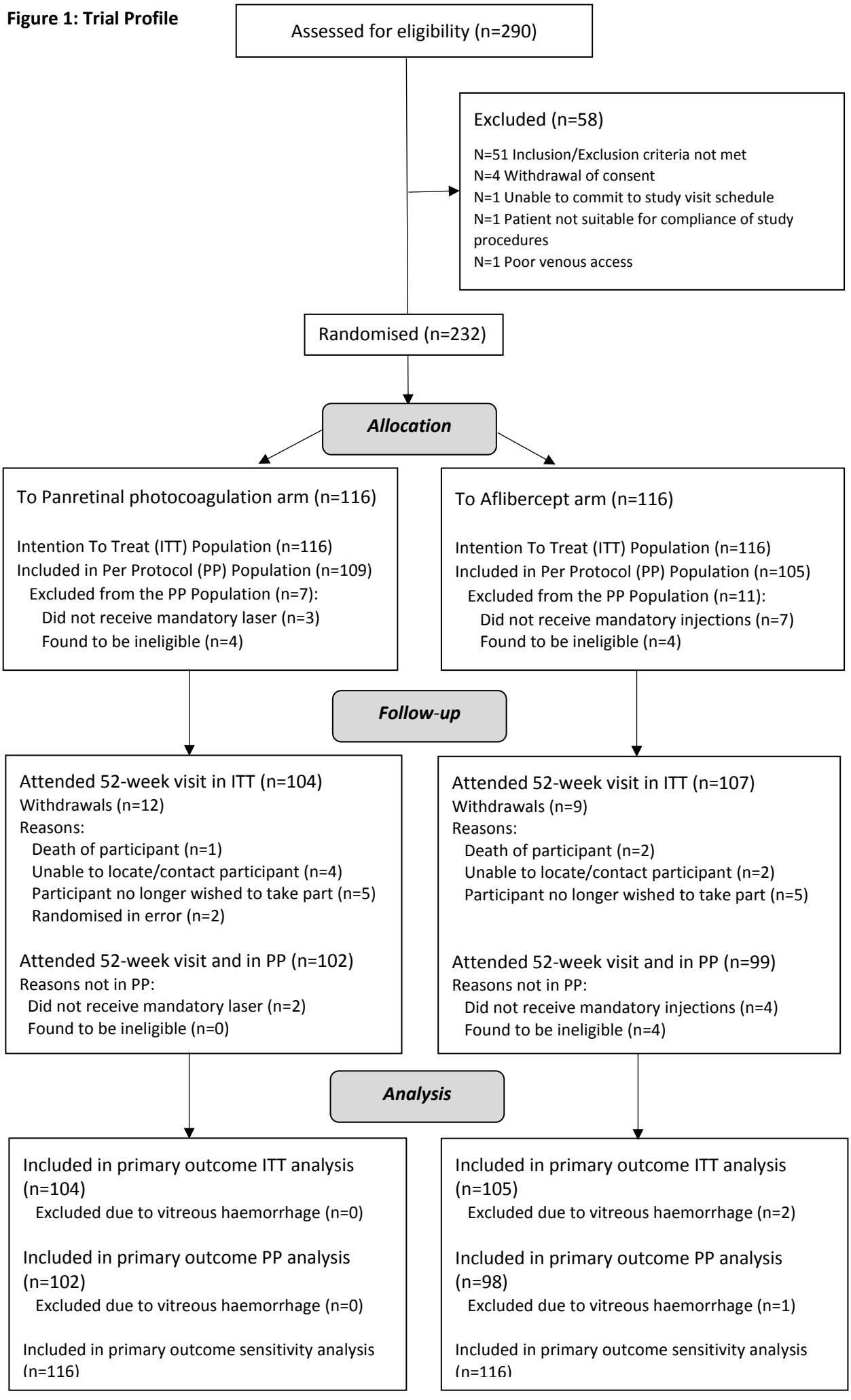

Table 1: Baseline characteristics in each arm

	PRP N=116	Aflibercept N=116
Mean (SD) age	50·8 (13·2)	51·5 (14·6)
Women % (n)	38% (44)	28% (33)
Diabetes Mellitus % (n)		
Type I	44% (51)	47% (54)
Type II	56% (65)	53% (62)
Medication % (n)		
Insulin only	46% (53)	53% (61)
Oral hypoglycaemic agents only	21% (24)	22% (26)
Insulin and oral hypoglycaemic agents	34% (39)	25% (29)
Diet controlled	0% (0)	0% (0)
Best corrected visual acuity % (n)		
54-69	9% (11)	9% (10)
≥70 ETDRS letters	91% (105)	91% (106)
Lens status (study eye) % (n)		
Clear lens	69% (80)	59% (68)
Visually insignificant Cataract	22% (26)	32% (37)
Visually significant Cataract	0% (0)	0% (0)
Pseudophakia	9% (10)	9% (10)
Macular oedema (study eye) % (n)		
No macular oedema	75% (87)	76% (87)
Non-central macular oedema	24% (28)	23% (27)
Central macular oedema	1% (1)	1% (1)
Mean (SD) Central subfield thickness	271·6 (28·1)	275·3 (30·9)[1]
Mean (SD) total volume (mm3)	8·94 (0·88)	8·99 (1·09)[1]
Proliferative Diabetic Retinopathy % (n)		
Naïve	54% (63)	52% (60)
Previously treated active PDR	46% (53)	48% (56)
Previous anti-VEGF therapy	4% (5)	5% (6)
Previous intravitreal steroid therapy	0% (0)	1% (1)
HbA1C % (n)		
Below 8% (below 63·90 mmol/mol)	38% (44)	35% (41)
8% to 10% (63·90 mmol/mol to 85·8 mmol/mol)	41% (48)	44% (51)
Above 10% (above 85·81 mmol/mol)	21% (24)	21% (24)
Blood pressure (Diastolic) % (n)		
≤90mmHg	88% (102)	87% (101)
>90mmHg	12% (14)	13% (15)

[1] The Optical Coherence Tomography (OCT) medical imaging was not done for one participant (withdrew at baseline).

Table 2: Comparison of Best Corrected Visual Acuity between arms at 12 and 52 weeks

Primary Outcome: BCVA	Mean (SD); N		Change from Baseline Mean (SE)		Adjusted difference between arms (95% CI)	*p*-value
	PRP	Aflibercept	PRP	Aflibercept		
Baseline	81·9 (8·0); 116	80·9 (8·3); 116	-	-	-	-
At 12-weeks						
ITT	81·3 (7·8); 101	82·6 (9·6); 109	-0·8 (0·4)	1·4 (0·5)	2·1 (0·5, 3·7)[1]	0·010
PP	81·3 (7·9); 99	82·7 (9·7); 102	-0·9 (0·4)	1·5 (0·6)	2·3 (0·6, 3·9)[2]	0·007
At 52-weeks						
ITT	79·1 (9·7); 104	82·4 (10·1); 105	-3·0 (0·7)	1·1 (0·6)	3·9 (2·3, 5·6)[1]	<0·0001
PP	79·3 (9·3); 102	82·6 (10·1); 98	-2·9 (0·7)	1·3 (0·6)	4·0 (2·4, 5·7)[2]	<0·0001

[1]The LME model incorporates 221 (109 PRP and112 aflibercept) participants with BCVA at either 12 or 52 weeks.
[2]The LME model incorporates 210 (106 PRP and 104 aflibercept) participants who have BCVA at either 12 or 52 weeks.