

Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial

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

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52 **Research in context**

53 **Evidence before this study**

54 Panretinal laser photocoagulation (PRP) is the standard of care for patients with
55 proliferative diabetic retinopathy (PDR). Currently, 3 anti-vascular endothelial growth
56 factor (anti-VEGF) therapeutic agents are administered by intravitreal injections to
57 treat ophthalmic conditions. Bevacizumab and ranibizumab are monoclonal
58 antibodies against VEGF A. Pre-CLARITY trial, we reviewed PubMed articles
59 between January 1st 2005 and January 31st 2014 and there were 8 short-term
60 randomised controlled trials (RCTs) comparing either bevacizumab or ranibizumab
61 monotherapy or in combination with PRP versus PRP alone in high risk PDR. These
62 RCTs showed new vessel regression with these agents after 3 to 4 months.

63 Aflibercept is the latest anti-VEGF agent and it blocks all isomers of VEGF A, B,
64 placental growth factor 1 and 2, and galectin-1. To date, there have been no RCTs on
65 aflibercept in PDR.

66 We updated the review on March 1st 2017. A well-designed multicentre clinical trial
67 comparing ranibizumab monotherapy versus PRP in patients with high risk PDR, with
68 and without macular oedema, has been published. Primary outcome of this RCT at 2
69 years showed non-inferiority of ranibizumab versus PRP in high risk PDR with a
70 median of 10 injections over 2 years (7 injections in the first year). However, this
71 RCT has not changed clinical practice worldwide due to the perceived difficulties
72 with practicalities of delivering repeated intravitreal injections in PDR patients and
73 the study only showed non-inferiority of BCVA to PRP albeit beneficial secondary
74 outcomes. Therefore, PRP remains the preferred choice.

75 In addition, a substantial proportion of patients after initial PRP are under long-term
76 follow-up in retinal clinics to identify and treat reactivation of existing
77 neovascularisation with supplemental PRP and these patients have been excluded
78 from previous clinical trials. Therefore, the role of anti-VEGF in this patient cohort
79 remains unclear.

80

81 **Added value of this study**

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

96

97 **Interpretation**

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

100

101

102 **Abstract**

103

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

108

109 **Methods:**

110 Adults with treatment naïve or post-laser treated active PDR from 22 UK ophthalmic
111 centres were recruited to this phase 2b, non-inferiority trial and randomly assigned
112 (1:1) to repeated intravitreal aflibercept or PRP standard care for 52 weeks.

113 Randomisation was by minimization using a web-based computer generated system.

114 Primary outcome assessors were masked optometrists. The treating ophthalmologists
115 and participants were not masked. The primary outcome was defined as a change in

116 best-corrected visual acuity (BCVA) at 52 weeks using a linear mixed-effects model

117 that estimated adjusted treatment effects at both 12 and 52 weeks, having excluded

118 fluctuations in BCVA owing to vitreous haemorrhage. This modified intention-to-

119 treat analysis was re-applied to the per protocol participants. The non-inferiority

120 margin was pre-specified as -5 letters. Safety was assessed in all participants. Trial

121 registration: ISRCTN32207582.

122

123 **Findings.**

124 We recruited 232 participants (116 per arm) between August 2014 and November

125 2015. 221 participants (n=112 aflibercept arm, n=109 PRP arm) contributed to the

126 modified intention-to-treat model, and 210 participants (n=104 aflibercept arm and

127 n=106 PRP arm) within per protocol. Aflibercept was non-inferior and superior to

128 PRP in both the modified intention-to-treat population (mean BCVA difference 3.9

129 letters; 95% CI 2.3-5.6 letters; $p < 0.0001$) and the per protocol population (difference

130 4.0 letters; 95% CI 2.4 -5.7 letters, $p < 0.0001$). There were no safety concerns.

131

132 **Interpretation.**

133 Intravitreal aflibercept in PDR results in improved outcome at 1 year compared to

134 PRP standard care.

135

136 **Funding**

137 The Efficacy and Mechanism Evaluation Programme, a Medical Research Council

138 and National Institute for Health Research partnership; Aflibercept was supplied by

139 Bayer Plc, Reading, UK.

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155 **phase IIb non-inferiority trial.**

156

157 **Introduction**

158

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

163

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

176

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

189

190 **Methods**

191 **Study design and participants**

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

195

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

201

202 Eligible patients with type 1 or 2 diabetes mellitus, aged 18 years or older, with clinical
203 evidence of treatment naïve PDR or persistent retinal neovascularization following
204 initial PRP requiring additional PRP (i.e. non treatment naïve) were included. Best
205 corrected visual acuity (BCVA) was ≥ 54 Early Treatment Diabetic Retinopathy Study
206 (ETDRS) letters, equivalent to 6/24 Snellen BCVA with sufficient media clarity and
207 pupillary dilatation for adequate fundus photographs. The fellow eye Snellen BCVA
208 was $\geq 2/60$. Women patients were using effective contraception, post-menopausal for \geq
209 12 months prior to trial entry, or surgically sterile. Study eye exclusion criteria were co-
210 existent ocular disease that affected or may affect visual acuity or prevent treatment
211 delivery. As diabetic macular oedema can co-exist with PDR and confound visual
212 acuity outcomes, all eyes with clinical evidence of diabetic macular oedema and
213 spectral domain optical coherence tomography central subfield thickness $\geq 300\mu\text{m}$ due
214 to macular oedema were excluded. Other ocular exclusions were moderate or dense
215 vitreous haemorrhage preventing clear visualisation of the macula and/or optic disc or
216 preventing laser treatment, fibrovascular proliferation or tractional retinal detachment
217 in the posterior pole, prior vitrectomy, other causes of retinal neovascularization, and
218 anticipated need for cataract extraction or vitrectomy within 12 months. Patients treated
219 with intravitreal anti-VEGF or steroid for DMO within 4 months or PRP within 8 weeks
220 prior to screening were excluded. Systemic exclusion criteria included haemoglobin
221 A1c (HbA1c) $\geq 12\%$, blood pressure $\geq 170/110$ mmHg and any medical condition that,
222 in the opinion of the investigator, precluded participation in the study. The clinical
223 assessments schedule is detailed in **table S1 and S2, appendix** and in the published
224 protocol.¹²

225

226 **Randomisation and masking**

227 Patients provided informed consent and those eligible were randomly allocated (1:1)
228 to either repeated intravitreal aflibercept 2mg/0.05ml (Bayer Pharma AG) or PRP
229 using the method of minimisation, concealed before allocation, stratified by site,
230 baseline PDR status (naïve versus non-naïve), BCVA (54-69 versus ≥ 70 ETDRS
231 letters), HbA1c ($< 8\%$ [$< 63.89\text{mmol/l}$], $\geq 8\%$ to $\leq 10\%$ [63.90 to 85.8mmol/mol] and
232 $> 10\%$ [$> 85.81\text{mmol/mol}$], diastolic blood pressure ($\leq 90\text{mmHg}$ versus $> 90\text{mmHg}$) by
233 collaborating site investigators via the King's Clinical Trials Unit web-based
234 randomisation service. Patients and clinical investigators were unmasked due to the
235 anatomical changes induced by the comparator. Outcome assessors including
236 optometrists, visual field technicians, imaging technicians and the Independent
237 Reading Centre were masked to treatment allocation. Primary outcome assessors
238 completed a treatment guess form to determine masking success.

239

240

241 **Procedures**

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

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

262

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

276

277 **Outcomes**

278 The primary outcome was BCVA letter change from baseline to 52 weeks in study eye
279 in the aflibercept arm relative to the PRP arm. A secondary outcome was BCVA change
280 from baseline to 12 weeks. Additional secondary visual function outcomes assessed at
281 52 weeks included unocular and binocular Esterman missed spots, binocular visual
282 acuity letter scores, low luminance visual acuity letter scores, categories of visual
283 acuity outcomes in terms of visual gain or loss, and contrast sensitivity letter scores.
284 Change from baseline between arms in patient reported outcomes using NEI-VFQ-25,
285 RetDQoL, RetTSQ at 52 weeks. Anatomical outcomes included new vessel regression
286 patterns and change in ETDRS diabetic retinopathy severity score levels at 12 and 52
287 weeks (**table S4, appendix**).¹³ The number of treatments required in both arms and
288 the proportion of patients requiring supplemental PRP in the aflibercept arm were
289 reported. We evaluated differences in ocular and systemic safety profile between arms
290 from baseline to 52 weeks.

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

294

295 **Statistical analysis**

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

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

329
330 Sensitivity to the missing at random assumption made in the primary outcome analysis
331 was undertaken in all randomised patients to assess sensitivity to the handling of
332 missing and excluded 52-week data, using three recommended scenarios affecting
333 either one or both arms.¹⁶ Sensitivity analysis was used to assess the use of concomitant
334 treatments, to assess changes to conclusions from inclusion of isolated outliers in
335 statistical analyses defined as exceeding four standard deviations from expected, and to
336 assess additional adjustment for all sites as a fixed effect.

337
338 Pre-planned subgroup analyses for primary outcomes were done by extending the
339 models to include interaction terms with arm for the randomisation stratifiers
340 including baseline visual acuity, HbA1c, diastolic BP and PDR status (naïve and non-
341 naïve).

342
343 The planned sample size was 220 participants. Detailed sample size calculations are
344 available in the published protocol. The SD of the change in visual acuity, after
345 adjustment for baseline, was anticipated to be 10.3, based on the estimate from a
346 relevant trial.¹⁷ In brief, the study had at least 90% power to detect non-inferiority of -
347 5 letters using a two-sided 95% confidence interval from an analysis of covariance
348 test with adjustment for baseline visual acuity.^{12, 16}

349 **Role of the funding source**

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

355

356 **Results**

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

360

361 Baseline characteristics were well balanced between treatment groups (**table 1**). A total
362 of 123 (53%) treatment naïve and 109 (47%) non-naïve patients were recruited. Mean
363 baseline BCVA was 81.4 (SD 8.1) ETDRS letters. The proportion of patients with
364 baseline BCVA 54-69 and ≥ 70 ETDRS letters were 9% and 91% respectively.

365

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

367 Patients included in the pre-specified Intention-to-Treat linear mixed effect model
368 were derived as follows: (1) The BCVA data were available for 211 patients of 232
369 randomly assigned patients (107 in aflibercept and 104 in PRP arms) at 52 weeks and
370 for 214 patients at 12-weeks (109 in aflibercept and 105 in PRP arm); (2) A total of 4
371 patients in the PRP arm at 12 weeks and 2 patients in the aflibercept arm at 52 weeks
372 were excluded due to presence of vitreous haemorrhage within 3 months of BCVA
373 recordings and BCVA was more than 3SD below the mean at that time point
374 (including all measurements); (3) There were 198 patients with BCVA available at
375 both 12 and 52 weeks. A total of 11 patients had BCVA recorded at 52 weeks and not
376 12 weeks (8 in PRP arm and 3 in aflibercept arm). In addition, there were 12 patients
377 who had BCVA recorded at 12 weeks but not at 52 weeks (5 in PRP and 7 in
378 aflibercept arm); (4) Therefore, there were 221 patients that contributed to the
379 analysis in the linear mixed effect model for the intention-to-treat strategy (109 in the
380 PRP arm and 112 in the aflibercept arm); (5) A total of 18 patients did not meet the
381 PP definition and were not included in the PP population (n=214). This included 11
382 (9.5%) patients in the aflibercept arm and 7 (6.0%) in the PRP arm), with 4 patients
383 in the aflibercept arm and 4 in the PRP arm not being compliant with the eligibility
384 criteria and a further 7 patients in the aflibercept arm and 3 in the PRP who did not
385 receive initial mandatory treatment requirements. Therefore, there were 210 patients
386 that contributed to the PP analysis in the LME model (106 in the PRP arm and 104 in
387 the aflibercept arm).

388

389 **Primary outcome**

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

394 Three sensitivity analyses on the population with completed follow-up at 52 weeks
395 were done, adjusting for sites, outliers and missing data. No patients were offered
396 anti-VEGF treatment for macular oedema in the PRP arm. So sensitivity analysis for
397 concomitant treatments was not required. When sites were considered, the adjusted
398 difference in BCVA between arms remained significant at 4.1 letters (95% CI 2.4 to
399 5.7), $p < 0.0001$, and 4.1 letters (95% CI 2.4 to 5.7), $p < 0.0001$, respectively in the

400 modified intention-to-treat and per protocol populations. A total of 207 and 198
401 patients remained after outliers in the modified intention-to-treat and per protocol
402 populations, defined as less than or more than 4SD were removed. This sensitivity
403 analysis showed the adjusted difference in BCVA between arms as significant at 4.0
404 letters (95% CI 2.7 to 5.4, $p<0.0001$) in the modified intention-to-treat and 4.1 letters
405 (95% CI 2.7 to 5.5, $p<0.0001$) in the per protocol population. The sensitivity
406 analysis for missing data also confirmed a superiority effect in both intention-to-treat
407 ($n=232$) and per protocol populations ($n=214$) for three pre-specified alternative
408 scenarios (**figure 2, appendix**).

409

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

411

412 **Secondary outcomes**

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

414

415 The proportion of patients with greater or equal to 10 letter improvement and able to
416 do so with baseline BCVA ≤ 90 was 5% (5/101) in the aflibercept arm compared to
417 2% (2/95) in the PRP arm (difference between arms was 2.8% (95% CI -3.1% to
418 9.1%, $p=0.45$). The proportion of patients with greater or equal to 10 letter worsening
419 was 5% (5/107) in the aflibercept arm compared to 15% (16/104) in the PRP arm
420 (difference between arms was 10.7%, 95% CI 2.6% to 19.3%, $p=0.009$). There were
421 5% (5/107) of patients with greater or equal to 15 letter worsening in the aflibercept
422 arm and 6% (6/104) in the laser arm (difference between arms was 1.1%, 95% CI (-
423 5.5% to 7.9%), $p=0.72$).

424

425 Binocular Esterman scores showed significant worsening with the PRP arm. This was
426 also reflected in lower binocular visual acuity scores in the PRP arm (**Table S7**).

427 Other visual function tests did not vary between arms. **Table S8** shows changes in
428 visual function in treatment naïve and non-naïve cohorts.

429

430 The RetDQoL scores (**table S9**) and NEI-VFQ scores (**table S10**) did not show
431 significant differences between arms. RetTSQ scores showed that patient satisfaction
432 scores were significantly better in the aflibercept arm and the adjusted mean
433 difference was 3.0 (95% CI 0.4 to 5.5, $p=0.022$) (**table S9**).

434

435 **Anatomical outcomes**

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

439

440 Treating investigators determined regression and reactivation patterns of retinal new
441 vessels to decide re-treatment based on pre-defined criteria. **Table S13** shows that a
442 significant proportion of eyes showed total regression of retinal new vessels in the
443 aflibercept arm compared to the PRP arm. The difference in proportions of total
444 regression favouring the aflibercept arm was 30% (95% CI 16% to 42%), $p<0.0001$ at
445 52 weeks.

446

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

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

458

459 **Treatment outcomes**

460 The proportion of patients that received treatment according to protocol was 94%
461 (109/116) in the aflibercept arm and 97% (113/116) in the PRP arm. The treatment
462 allocation guess form, measuring success of masking of primary assessors to
463 treatment allocation, was reported for 210 participants. Assessors guessed correctly
464 for 15% (32/210), incorrectly for 10% (20/210), and were unable to tell for 75%
465 (158/210) of participants.

466

467 By 52 weeks, aflibercept arm patients received a mean (SD) of 4.4 (1.7) injections,
468 (95% CI 4.1 to 4.7), [Median (IQR) 4.0 (3.0 to 5.0)] including the 3 mandated
469 loading doses. The mean number of aflibercept injections in treatment naïve patients
470 was 4.6 (1.6) [Median (IQR) 4 (3, 6)] while non-naïve patients received a mean
471 number of injections 4.1 (1.8), [Median (IQR) 4.0 (3.0 to 4.8)]. A total of 2 (1.6%)
472 patients required supplemental PRP in the aflibercept arm.

473

474 In the PRP arm, 78 (69%) received multispot laser and the remaining received single
475 spot laser. The type of laser delivery was not recorded for 3 patients. Distribution of
476 PRP session numbers required were 1 session in 35 eyes (30.2%); 2 sessions in 25
477 eyes (21.6%), 3 sessions in 10 eyes (8.6%), 4 sessions in 4 eyes (3.4%) and 5
478 sessions in 1 eye (0.9%). From week 12, 75 patients (65%) in the PRP arm required
479 supplemental PRP. The mean number (SD) of supplemental PRP sessions required
480 was 1.17 (1.16), 95% CI (0.96 to 1.38) with the treatment naïve patients requiring
481 1.35 (1.28) sessions and in the non-naïve arm, the mean was 0.96 (0.96).

482

483 **Safety outcomes**

484 When comparing other complications of PDR between arms, incidence of vitreous
485 haemorrhage was higher in the PRP arm (p=0.034). The proportion of patients
486 requiring vitrectomy was small and not significant between arms (p=0.066). There
487 were no cases of endophthalmitis in the study eye (**table 3**).

488

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

495

496 **Discussion**

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

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

505

506 Superior treatment satisfaction scores in the aflibercept arm were unexpected but
507 highlighted patients' preference for this therapy. The lower incidence of centre-
508 involving macular oedema and vitreous haemorrhage observed in the aflibercept arm
509 may have contributed to both the mean BCVA improvement and patient preference as
510 these conditions are the most common causes of symptomatic visual impairment in
511 patients with PDR. The proportion of patients with no macular oedema at 52 weeks
512 was 89% (93/105) in the aflibercept arm compared to 71% (74/104) in the PRP arm.
513 The incidence of vitreous haemorrhage was twice as high in the PRP arm (18%
514 (21/116) compared to 9% (10/116) in the aflibercept arm).

515

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

520

521 The superior BCVA findings were supported by significantly better binocular visual
522 acuity and binocular Esterman scores in the aflibercept arm. These observations have
523 significant impact on eligibility to retain a driving licence. In the UK, the Driver and
524 Vehicle Licensing Agency (DVLA) have designated both a minimum visual acuity
525 and Esterman visual field standard to maintain a valid driving licence.²¹ With
526 advances in laser technology and techniques, there are reports with short follow-up
527 suggesting that modern-day laser techniques and technology such as multispot laser
528 have reduced the prevalence of visual field loss with PRP.^{6,21,22} However, our study
529 shows that despite 69% of the study cohort being treated with multispot laser,
530 aflibercept is associated with lower risk of visual field loss than modern day laser at
531 52 weeks, in keeping with findings noted in the recent ranibizumab trial in PDR at 2
532 years.¹⁰

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

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

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

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

554

555 The robust RCT design, high statistical power and excellent retention rates are
556 particular strengths of this study. The study patients are representative of PDR
557 population, therefore these findings can be generalised to clinical practice for the first
558 year of therapy. Re-treatment criteria used in CLARITY are very similar to those
559 followed in the ranibizumab trial¹⁰ and determined by treating investigators at each
560 study visit. Compliance with treatment (94% aflibercept arm and 97% PRP arm) was
561 very good in CLARITY, indicating that these re-treatment criteria can be easily
562 applied to routine clinical practice.

563

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

566

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

573

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

580

581

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658
659
660

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662

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687

688 **Author Contribution**

689 The study was conceived by the Chief Investigator (SS) and co-lead (PH). The study
690 was designed by the grant co-applicants (SS, PH, AP; JK; CM; RTE; JB; PH; DH).
691 King's Clinical Trial Unit core team: AR, JK, CM; AR: Trial Manager. AP and JV
692 provided the statistical input. SS drafted the manuscript and all authors commented on
693 drafts and approved the final version.

694 Collaborators listed acted as coordinators of the trial at each clinical site and recruited
695 and managed patients (AB, BB, UC, HE, TE, RG, SG, MH, SK, AL, MM, LM, GM,
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710

711 **Drug supply**

712 Aflibercept was provided by Bayer Plc, Reading, UK in accordance with its marketing

713 authorisation. The Clinical Trials Manufacturing and Supplies Department, Pharmacy

714 Production Department, Royal Free Hospital NHS Foundation Trust, was responsible

715 for packaging, labelling and QP releasing the drug prior to distribution to site.

716

717 **Conflicts of interest**

718 SS has received research grants, travel grants, speaker fees and attended advisory

719 board members of Novartis, Bayer, Allergan and Roche. PH has received research

720 grants, travel grants, speaker fees and attended advisory board members of Novartis,

721 Bayer, Allergan. The other named authors declare that they have no competing

722 interests.

723

724