Efficacy and safety of ranibizumab with or without panretinal laser photocoagulation versus laser photocoagulation alone in proliferative diabetic retinopathy – the PRIDE study

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ABSTRACT.
Purpose: Panretinal photocoagulation (PRP) is the current standard of care in proliferative diabetic retinopathy (PDR). However, treatment with anti-vascular endothelial growth factor agents might offer better patient outcomes with fewer side-effects. The PRIDE study aimed to assess the efficacy and safety of ranibizumab with or without PRP compared with PRP alone in patients with PDR.
Methods: A total of 106 PDR patients without diabetic macular oedema were randomized to receive ranibizumab 0.5 mg monotherapy (n = 35), PRP (n = 35) or combined ranibizumab 0.5 mg/PRP (n = 36). The primary objective of this 12-month, multicentre, phase II study was to investigate the change in area of retinal neovascularization (NV). Complete regression of leakage and best-corrected visual acuity (BCVA) were key secondary end-points.
Results: At Month 12, there was a statistically significant difference of –2.83 mm² in the least square mean change in NV area between the ranibizumab monotherapy and PRP group, favouring ranibizumab (95% CI [–5.45; –0.21], p = 0.0344). At Month 3, 67%/0%/67% of the patients in the ranibizumab/PRP/combination groups, respectively, showed complete regression of leakage from NVs, while at Month 12, 28%/8%/18% showed complete regression of leakage from NVs. BCVA change was greater in the ranibizumab group compared with the PRP monotherapy group at Month 12 (+1.6 letters; 95% CI [−2.3; 5.5] versus −3.9 letters; 95% CI [−7.8; −0.1], p = 0.0495).
Conclusions: Ranibizumab monotherapy is an alternative treatment option to laser treatment in patients with PDR. Ranibizumab showed stronger effects on NV leakage and area reduction while offering better visual acuity results than PRP alone.

Key words: anti-VEGF therapy – panretinal laser photocoagulation – PRIDE study – proliferative diabetic retinopathy – ranibizumab – retinal neovascularization

Introduction
Diabetic retinopathy (DR) is a common microvascular complication of diabetes mellitus occurring in one-third of the 285 million diabetic patients worldwide (Yau et al. 2012). Approximately 7% of patients with diabetes develop the more severe sight-threatening proliferative diabetic retinopathy (PDR) (Wong et al. 2011; Yau et al. 2012), which is characterized by the growth of new, abnormal vessels on the retina or optic disc. If left untreated, PDR can result in severe vision loss (DRS Research Group 1981).

Since the 1980s, panretinal photocoagulation (PRP) therapy has been the treatment modality of choice in PDR (DRS Research Group 1981). PRP laser treatment targets areas of retinal ischaemia thereby reducing oxygen demand in the retina and preventing the development of neovascularization (NV) (Ting & Wong 2017). Unfortunately, PRP is associated with deleterious side-effects, most notably a diminished field of vision owing to the destructive nature of the treatment, and a decrease in vision owing to an increase in macular oedema (Fong et al. 2007).

Ranibizumab is a recombinant, humanized, monoclonal antibody fragment that selectively binds and inhibits all active forms of vascular endothelial
growth factor (VEGF)-A, the angiogenic protein responsible for NV in many ischaemic retinal diseases including PDR (Aiello et al. 1995). Evidence suggests that anti-VEGF therapy could complement or even replace the use of PRP in PDR (Fong et al. 2007; Subash et al. 2016). Previous randomized clinical trials have found that ranibizumab is at least as effective as PRP in patients with PDR and results in fewer side-effects such as worsening of visual field, development of macular oedema or the need for vitrectomy, in addition to its strong safety profile (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015; Figueira et al. 2016). Figueira et al. assessed the regression of NV and reported that ranibizumab either alone or in combination with PRP was as effective as PRP monotherapy in a small study population (Figueira et al. 2016). The DRCR.net Protocol S study demonstrated that visual acuity outcomes in PDR were non-inferior for patients treated with ranibizumab compared with those treated with PRP alone (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015). However, in the Protocol S study, eyes with centre-involving diabetic macular edema (DME) were included and these eyes could receive ranibizumab regardless of their randomization group (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015).

The PRIDE study is the first study designed to assess the efficacy and safety of ranibizumab with or without additional PRP compared to PRP monotherapy in patients with PDR but without DME.

Materials and Methods

The PRIDE study (NCT01594281) is a 12-month, phase II, multicentre, open-label (but reading centre-blinded), randomized, active-controlled clinical trial. The study adhered to the tenets of the Declaration of Helsinki (World Medical Association 2013) and was approved by all institutional review boards at the participating centres and health authorities.

Patient population

Key inclusion criteria were PDR secondary to type 1 or type 2 diabetes under medical surveillance/with stabilized treatment, age ≥18 years, best-corrected visual acuity (BCVA) ≥20 ETDRS letters (Snellen equivalent 20/400) and HbA1c ≤12%. Key exclusion criteria were clinically significant DME with centre involvement, large areas of NV (≥2 disc areas) within the macula, proliferative vitreoretinopathy (PVR), severe vitreous haemorrhage impairing imaging/treatment, previous treatment with PRP (>300 laser burns within the previous 6 months), treatment with anti-VEGF within the past 3 months and treatment with corticosteroids within the past 6 months. Eligibility screening was performed by the Reading Center.

Examination

Best-corrected visual acuity was assessed on a monthly basis using the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score. Safety events were monitored and recorded by the study sites at every monthly visit. In addition, an independent Data Safety Monitoring Board reviewed all safety related issues on a regular basis (every 4 months during the recruitment phase; every 6 months until the end of the core study phase). Colour fundus photography, fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD-OCT) images were captured according to a standard protocol. Patients underwent wide-field (50°–60°) colour fundus photography and FA imaging at screening, Months 3 and 12. Screening images were used for baseline analysis. Images were captured using an 8-field protocol (Fig. 1, modified from the ETDRS 7 standard fields (ETDRS 1991d)) with multiple angiographic stereoscopic frames of field 2 captured during the transit phase, mid-phase (<3 min) and late phase (5–10 min); in addition, peripheral images were captured during the mid-phase as well as in the late phase. If available, ultra-wide-field FA (102°) was performed instead using a modified protocol. The imaging system used for each patient remained constant throughout the study.

SD-OCT volume scans (20° × 20°), centred on the fovea, were obtained at baseline, Months 3, 8 and 12.

Photographer certification was required prior to capturing images for the study.

Image analysis

Colour fundus photography, FA and SD-OCT images were analysed by certified graders at the Cologne Image Reading Center (CIRCL, Cologne, Germany) using a two-grader system. Discrepancies were solved by open adjudication. Graders were masked to the treatment group.

SD-OCT analysis included qualitative assessment of macular oedema, subretinal fluid, epiretinal membranes and vitreomacular traction, as well as manual, error-corrected measurement of mean central subfield thickness (neurosensory retina plus subretinal fluid) using computer-assisted manual grading software. SD-OCT was mandatory at baseline, Months 3, 8 and 12. Additional OCT was performed at investigators discretion and only uploaded to the central reading centre if a significant change in pathology was detected.

Composite images were manually created from the 8 captured early/mid-phase FA fields using Adobe Photoshop (Version 9, San Jose, CA, USA). Images were carefully selected to ensure that similar time frames were used during follow-up. Care was taken that NVs did not appear twice on the composite, that NVs were not hidden by a dark area of another frame (if necessary, parts of overlying image frames were cut out) and that NVs did not spread over adjacent image frames wherever possible. NVs not captured completely, and NVs in areas not captured on either screening or Month 12, were not considered for quantitative analysis. FA composites were viewed and graded using grading software equipped with standard planimetric tools to allow calculation of the area of any closed-loop structure manually drawn by the grader. Area of active NV (neovascularization elsewhere [NVE] plus neovascularization of the disc [NVD]) and area of blocked fluorescence potentially obscuring NV were quantified using the early/mid-phase composite at baseline, Months 3 and 12. Greatest line dimension (GLD) of horizontal and vertical reference areas were calculated additionally to ensure valid assessment of area measurements during follow-up. Qualitative analysis of FA images included the presence and number of NVE and the presence of NVD, development of new NV during follow-up compared with baseline, complete regression of leakage from NV and macular ischaemia (capillary loss within the foveal central...
subfield according to ETDRS Report No. 11) (ETDRS 1991a). The severity level of DR was determined using the ETDRS severity scale (ETDRS 1991b); however, in contrast to the original ETDRS severity scale, wide-field FA images captured according to a modified 8-field photographer’s protocol were used in addition to colour fundus photography for identification of NVs. Prior PRP treatment was not considered for determining the severity level. Thus, during follow-up, eyes with PRP but without any evidence of NVs or fibrous proliferation were classified as non-proliferative diabetic retinopathy (NPDR) for the purpose of this study.

Treatment

Patients in the ranibizumab and combination groups received at least three initial monthly intravitreal injections of ranibizumab 0.5 mg. Further injections were given monthly until stability of morphological parameters was reached, as determined by the Investigator, that is no further improvement of morphology or no worsening of morphology (inactive NVs) was seen over three consecutive months while on ranibizumab treatment as assessed by ophthalmoscopy and, if applicable, FA. In the PRP monotherapy and combination groups, 1200–1600 laser spots (500 μm spot size at the retina) were applied in three sessions between baseline and Month 3. If worsening or reperfusion of NVs occurred or new NVs were detected by the Investigator, retreatment was initiated with at least two monthly ranibizumab injections and/or 500 additional laser spots, depending on the treatment group. PRP rescue treatment was allowed in this study and was possible for patients in the ranibizumab monotherapy group beginning at Month 2 (after two injections of ranibizumab), and only if a sufficient progression of NV, with associated threat to visual loss, was evident.

Statistical analysis

The full analysis set (FAS) comprised all randomized patients who received at least one application of study treatment and who underwent at least one post-baseline assessment. Following the intent-to-treat (ITT) principle, patients were analysed according to the treatment assigned; no patients were excluded from the FAS because of protocol deviations.

The primary outcome was the change in total area of NV [mm²] (calculated as sum of area of NVE and NVD) on FA early/mid-phase frames from baseline to Month 12. Primary analysis was repeated on the per protocol set (PPS), which excluded patients with relevant protocol violations, to serve as a sensitivity analysis assessing robustness of the results. Secondary outcomes included change in best-corrected visual acuity, complete regression of leakage from NV, change in the ETDRS severity scale stage, change in central subfield thickness, treatment frequency over the course of the study and safety. For the primary outcome, treatments were compared by an analysis of covariance (ANCOVA) model with baseline area of NV as a covariate. All quantitative secondary outcomes (i.e. BCVA, central subfield thickness) were analysed with ANCOVA models using the respective baseline parameters as covariates. Data included for analysis were based on the last observation carried forward (LOCF). The focus of this proof of clinical concept study was not on hypothesis testing, and thus, p-values are to be read descriptively.

Results

Out of the 108 patients randomized, two patients withdrew before the start of treatment. Consequently, the FAS and safety set included 106 patients. Patients in the FAS were allocated to receive ranibizumab monotherapy (n = 35), PRP (n = 35) or combined ranibizumab + PRP (n = 36) (Fig. 2).

Baseline characteristics

The baseline characteristics of all patients enrolled in the study are outlined in Table 1. The mean (± SD) patient age was 53.5 ± 12.1 years, with 68.9% male and 31.1% female. The proportion of patients with type 1 and type 2 diabetes was 43.4 and 56.6%, respectively. The mean (± SD) duration of diabetes was 22.9 ± 11.4 years. One patient in the ranibizumab group received panretinal laser treatment prior to study entry, but fewer than 250 laser burns were applied.

Mean (± SD) area of NV at baseline was higher in the ranibizumab monotherapy group (9.39 ± 15.41 mm²) compared with 5.40 ± 9.68 mm² in the PRP monotherapy group and 4.08 ± 7.08 mm² in the combination group). There was no difference regarding modified ETDRS severity scales between groups at baseline.

Treatment during follow-up

In the ranibizumab group, patients received a mean (± SD) of 5.2 ± 2.3 injections over the 12-month study period (median = 5.0, range 1–10). Patients in the PRP group received on average 1919 ± 673 PRP laser spots during the 12-month study period. Patients in the combination group received a mean (± SD) of 5.0 ± 2.2
injections and 1670 ± 568 PRP laser spots. Between Month 3 (after the ranibizumab loading phase) and Month 12, patients in the ranibizumab group received a mean (± SD) of 2.3 ± 2.1 injections, whereas patients in the combination group received a mean (± SD) of 2.1 ± 2.1 injections. Four patients in the ranibizumab group (11%) received one rescue laser therapy during the 12-month study period. Five patients in the ranibizumab group (11%) received one rescue laser therapy during the 12-month study period. Five patients in the ranibizumab group (11%) received one rescue laser therapy during the 12-month study period. Five patients in the ranibizumab group (11%) received one rescue laser therapy during the 12-month study period. Five patients in the ranibizumab group (11%) received one rescue laser therapy during the 12-month study period.

**Fig. 2.** Patient recruitment, randomization and dropout. Of the 153 patients screened, 45 did not meet the inclusion criteria (randomized set [n = 108]); 2 patients were not included in the full analysis set and safety set (n = 106) because they withdrew before first treatment was given; 23 patients of the FAS discontinued the study prior to Month 12 with 7 patients not having a post-baseline (post-BL) fluorescein angiography. Reasons for discontinuation were as follows: adverse events (n = 12); protocol violation (n = 1); lost to follow-up (n = 6); and death (n = 4). PRP, panretinal laser photocoagulation.

**Table 2.** The number of vitrectomies is outlined in prior to vitrectomy. The details of all combination group had a vitrectomy group. One of the three patients in the combination group developed new NVD during follow-up (compared with none in the PRP group) (Table 3). Figure 4 shows two examples of NV assessment and change over the study period.

Complete regression of NV leakage at Month 3 was observed in 66.7, 0.0 and 66.7% of patients in the ranibizumab group, the PRP group and the combination group, respectively (Table 3). There were statistically significant differences in rates of complete regression of NV leakage between the ranibizumab group and the PRP group (p < 0.001) and between the combination group and the PRP group (p < 0.001). Complete regression of NV leakage at Month 12 was observed in 27.6, 7.7 and 17.9% of patients in the ranibizumab, PRP and combination groups, respectively (Table 3). No statistically significant difference in the rates of complete regression of NV leakage was observed between groups at Month 12. Blocked fluorescence with the potential to obscure NVs on FA was observed in only very few cases (Table 1 [baseline values] and Table 3 [values for Months 3 and 12]).

In patients who did not show complete regression of NV leakage at Month 12, the mean (± SD) duration between their last injection and the end of the study was 169 (± 105) days in the ranibizumab group and 168 (± 121) days in the combination group. The mean (± SD) duration between last laser treatment and the end of the study was 196 (± 146) days in the combination group and 195 (± 127) days in the PRP group.

Conversely, in patients who did demonstrate complete regression of NV leakage at Month 12, patients in the ranibizumab and combination groups received their last injection 51 (± 42) days and 80 (± 92) days before the end of the study, respectively. The mean (± SD) duration since last laser treatment was 127 (± 134) days in the combination group and 221 (± 193) days in the PRP group.

Across all groups at baseline, 28% of patients showed mild PDR, 45% moderate PDR and 26% high-risk PDR (Table 1). A considerable number of

### Area of neovascularization

Between baseline and Month 12, the mean (± SD) area of NV decreased from 9.39 ± 15.41 mm² to 2.70 ± 4.11 mm² in the ranibizumab group, from 5.40 ± 9.68 mm² to 4.58 ± 11.39 mm² in the PRP group and from 4.08 ± 7.08 mm² to 1.96 ± 4.91 mm² in the combination group. There was a statistically significant difference of −2.83 mm² in the least square (LS) mean change in NV area between the ranibizumab monotherapy and PRP groups, favouring the ranibizumab group (95% CI [−5.45; −0.21], p = 0.0344, Fig. 3). No difference was detected in the LS mean change in NV area between the combination and the ranibizumab groups (LS mean difference −1.17 mm², 95% CI [−3.81; 1.47], p = 0.3809) or the combination and the PRP groups (LS mean difference 1.66 mm², 95% CI [−0.96; 4.28], p = 0.2113). Analysis was adjusted for baseline NV area (ANCOVA). Similar results were seen in the sensitivity analysis using the PPS, thus showing the robustness of these results.

At Month 3, the number of patients developing new NVE was as follows: one in the ranibizumab group, six in the PRP group and none in the combination group (Table 3). At Month 12, new NVE compared with baseline were detected in seven patients in the ranibizumab group, eight patients in the PRP group and seven patients in the combination group. One patient in both the ranibizumab group and the combination group developed new NVD during follow-up (compared with none in the PRP group) (Table 3).
patients in the ranibizumab and combination groups demonstrated complete regression of leakage from NV, as well as the absence of fibrous proliferation during follow-up on FP and FA, and thus improved to NPDR staging in our study. In the ranibizumab group (combination group), 49% (52%) of patients were staged as NPDR at Month 3 and 14% (14%) at Month 12. In the PRP group, 0% of patients were graded as NPDR at Month 3 and only 4% at Month 12. At the same time, the proportion of patients with high-risk PDR in the ranibizumab group decreased from 26% at baseline to 6% at Month 3 and 17% at Month 12. In the PRP group, there was a small difference between baseline and Month 3 (29 and 26%), but a decrease to 12% at Month 12. In the combination group, high-risk PDR decreased from 25 to 9% at Month 3 and 0% at Month 12 (Fig. 5). For patients with high-risk PDR at baseline, the shifts in ETDRS severity levels from baseline to Months 3 and 12 are presented in Table 3. Full shift tables showing changes in all stages of diabetic retinopathy between baseline and Months 3 and 12 are presented in Table S2.

**BCVA**

In the ranibizumab group, mean (± SD) BCVA increased from 83.3 ± 7.4 letters at baseline to 84.4 ± 8.6 letters at Month 12. Mean (± SD) BCVA decreased from 80.5 ± 8.3 letters at
Table 2. Study treatments, by group.

| Treatment | Ranibizumab | Panretinal laser | Combination |
|-----------|-------------|-----------------|-------------|
| n (%) of patients receiving rescue treatment with PRP after Month 3 | 4 (11.4%)† | N/A | N/A |
| Mean (SD) number of injections after initial injections | 2.3 (2.1) | N/A | 2.1 (2.1) |
| PRP laser spots, mean (SD) | N/A† | 1919.4 (673.1) | 1670.0 (568.4) |
| PRP laser spots after Month 3, mean (SD) | N/A† | 878.8 (630.5) | 759.7 (530.2) |
| PRP – panretinal laser photocoagulation, SD = standard deviation. Rescue treatment with anti-VEGF injections was not permitted in the study and led to discontinuation from further study treatment. However, patients who discontinued the study prior to Month 12 (e.g. due to CSME) could receive anti-VEGF injections after dropout. All reasons for patient dropout during the study period are outlined in Table S1. Please note that PRP rescue treatment was allowed in the study and was not considered for the calculation of mean PRP laser spots in this table. The 4 patients with PRP rescue treatment in the ranibizumab monotherapy group received a mean ± SD of 1342.5 ± 295.7 laser spots. |

Baseline to 76.8 ± 17.0 letters at Month 12 in the PRP group, and from 80.0 ± 9.5 letters at baseline to 78.9 ± 12.2 letters at Month 12 in the combination group. There was a difference in LS mean BCVA change of 5.5 letters (95% CI [0.0, 11.0], p = 0.0495) between the ranibizumab group and the PRP group, in favour of ranibizumab (Fig. 6). There was a non-significant difference of 3.0 letters (95% CI [-2.5; 8.5], p = 0.2767) between ranibizumab and the combination group. Similarly, there was a non-significant difference of -2.5 letters (95% CI [-7.9; 2.9], p = 0.3641) between the PRP group and the combination group.

Central subfield thickness

Mean (± SD) central subfield thickness (CST) decreased by 6.0 ± 15.1 μm in the ranibizumab group and increased by 36.2 ± 55.9 μm and 17.6 ± 46.7 μm in the PRP and combination groups, respectively, from baseline to Month 12 (Table 3). The LS mean difference of -40.7 μm between the ranibizumab group and the PRP group was statistically significant (95% CI [-62.1; -19.3], p = 0.0003), as the difference of -22.9 μm between the ranibizumab group and the combination group (95% CI [-44.2; -1.6], p = 0.0357, Fig. 7). There was no statistically significant difference in CST LS mean change between the PRP group and the combination group (95% CI [-3.7; 39.3], p = 0.1034). At Month 12, none of the patients in the ranibizumab group, but 10 patients (32.3%) in the PRP group and 4 patients (12.9%) in the combination group, demonstrated a CST of 300 μm or higher.

Change in modified ETDRS severity scale

There was no statistically significant difference between treatment groups in terms of change in modified ETDRS severity scales between baseline and Month 12 (Fig. 5).

Safety

The rate of cardiovascular adverse events (AEs) was low as shown by the Anti-Platelet Trialists Collaboration (APTC) events presented in Table 4. Reasons for patient dropout during the study period are outlined in Table S1. Key ocular serious adverse events (SAEs) and vitrectomies as reported by the investigator are presented in Table S3. Ocular AEs and non-ocular SAEs are presented in Tables S4 and S5, respectively. No new safety findings for either ranibizumab or PRP were reported.

Discussion

There is growing evidence suggesting that anti-VEGF therapy has a beneficial effect on visual and morphological outcomes in PDR. To date, limited data are available regarding differences in the treatment effects of anti-VEGF therapy and PRP therapy on NV. Similarly, data on NV recurrence during follow-up and the effect of anti-VEGF therapy in eyes without DME are lacking. The PRIDE study was designed to add clarity on the efficacy of ranibizumab in PDR, either alone or in combination with PRP, in patients without DME.

We report that ranibizumab monotherapy was more effective than PRP in reducing the area of NV between baseline and Month 12 in patients with PDR. At Month 3, both ranibizumab and a combination of ranibizumab plus PRP were significantly more effective than PRP monotherapy at reducing NV area, however, this significance did not persist up to Month 12 for the combination group. The observed increase in NV area in the combination group between Months 3 and 12 is noteworthy. Indeed, a similar increase was also seen in the PRP group during this period, a possible explanation for which may be an increase in disease activity as a side-effect of the PRP treatment. Such side-effects including development of macular oedema have been documented previously in a minority of patients following laser treatment (McDonald & Schatz 1985;
In comparison, eyes in the large (n = 394 study eyes), multicentre, randomized, controlled Protocol S study, who were randomized into the ranibizumab group, received six initial injections in 4-week intervals (with deferral of the last two injections allowed in case all neovascularization had resolved). Further injections were given every 4 weeks unless neovascularization was absent or stable over three consecutive visits (decision to re-inject was at investigator discretion). This treatment protocol resulted in a median of 7 injections in eyes without DME at baseline and 9 injections in eyes with DME at baseline in Year 1 of that study. (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015).

Regarding the visual outcomes from PRIDE, our study found a difference in BCVA change of +5.5 letters between the ranibizumab group and the PRP group from baseline to Month 12. This difference favoured the ranibizumab-treated patients and was driven largely by a loss of vision in the PRP group, possibly related to the detected increase in CST in this group. This visual outcome data are consistent with the reported findings from Protocol S (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015). The primary outcome of the Protocol S study was mean BCVA change at 2 years (5-letter non-inferiority margin). It should be noted that, unlike the current study, the presence of centre-involving DME was not an exclusion criterion in Protocol S, and a total of 53% of eyes in the PRP group of Protocol S received additional ranibizumab injections during the 24-month follow-up.

In the Protocol S study, ranibizumab resulted in visual acuity gains of +2.8 letters compared with +0.2 letters gained in the PRP treatment group at 2 years. Among eyes without DME at baseline in Protocol S, mean change in visual acuity letter score differed by +1.4 letters between the ranibizumab and PRP groups. More recently, the 5-year follow-up data from Protocol S have been published. Similar BCVA gains were reported between the ranibizumab and PRP groups at Year 5 (3.1 and 3.0 mean letter gain from baseline, respectively). The mean change in cumulative visual field total point score favoured the ranibizumab arm (−330 dB versus −527 dB in the PRP group). Of note, while fewer eyes in the ranibizumab

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Table 3. Morphological and visual outcomes.

|                       | Ranibizumab (n = 35) | Panretinal Laser (n = 35) | Combination (n = 36) |
|-----------------------|----------------------|--------------------------|---------------------|
| Change in sum of NV area (NVD and NVE), mean (SD) |                       |                          |                     |
| Month 3               | −5.87 (12.66)        | −0.73 (2.79)             | −2.67 (3.92)        |
| Month 12              | −4.60 (11.33)        | −0.94 (3.92)             | −1.74 (3.00)        |
| Patients with development of new NVE during follow-up (compared to baseline), n (%)* |                       |                          |                     |
| Month 3               | 1 (3.0)              | 6 (19.4)                 | 0 (0.0)             |
| Month 12              | 7 (24.1)             | 8 (30.8)                 | 7 (25.0)            |
| Blocked fluorescence (BF) potentially obscuring NV on FA by visit and treatment, n (%) |                       |                          |                     |
| Month 3               | 3 (9.1)              | 6 (19.4)                 | 4 (12.1)            |
| Month 12              | 4 (13.8)             | 1 (3.8)                  | 0 (0.0)             |
| Complete resolution of leakage from NV, n (%)‡ |                       |                          |                     |
| Month 3               | 0.0 (0.0)            | 0.0 (0.0)                | 0.0 (0.0)           |
| Month 12              | 0.0 (0.0)            | 1 (3.6)                  | 0.0 (0.0)           |
| Change in sum of NV area (NVD and NVE), mean (SD) |                       |                          |                     |
| Month 3               | −1.1 (7.3)           | −3.7 (17.1)              | −1.1 (7.8)          |
| Month 12              | 6.0 (15.1)           | 36.2 (55.9)              | 17.6 (46.7)         |

*Percentages presented refer to the respective number of valid observations in the full analysis set. Driver of both the ranibizumab and combination groups. Patients in these groups received a mean of 2.3 and 2.1 injections between Month 3 (after the ranibizumab loading phase) and Month 12, with their last injection received on average 4.4 and 5.0 months prior to the end of the core study period in the ranibizumab and the combination group, respectively. Additionally, the mean duration since the last injection was shorter in patients who demonstrated complete regression of NV leakage than in those patients who still displayed active NV at Month 12, in both the ranibizumab and the combination groups.

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Dogo et al. 1999; Soman et al. 2012). Of note, 32.3% of patients in the PRP group demonstrated macular oedema (defined here as CST ≥300 μm) at Month 12 (ranibizumab group: 0.0%; combination group: 12.9%).

It seems plausible to suggest that there was under-treatment with ranibizumab in both the ranibizumab group and the combination group. Patients in these groups received a mean of 2.3 and 2.1 injections between Month 3 (after the ranibizumab loading phase) and Month 12, with their last injection received on average 4.4 and 5.0 months prior to the end of the core study period in the ranibizumab and the combination group, respectively. Additionally, the mean duration since the last injection was shorter in patients who demonstrated complete regression of NV leakage than in those patients who still displayed active NV at Month 12, in both the ranibizumab and the combination groups.

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For ‘Change in NV area’ and ‘Change in CST’, values presented are raw means.

*Percentages presented refer to the respective number of valid observations in the full analysis set.

1PRP treatment was not considered for staging, thus eyes with neither NV leakage nor fibrous proliferation could receive NPDR staging during follow-up. There was no shift of high-risk PDR to DR absent (10), questionable DR (14, 15) or CG (90).

2Expanded shift tables including other DR categories at baseline are presented in Table S2.

3Total§ includes patients and was driven largely by a loss of vision in the PRP group, possibly related to the detected increase in CST in this group. This visual outcome data are consistent with the reported findings from Protocol S (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015). The primary outcome of the Protocol S study was mean BCVA change at 2 years (5-letter non-inferiority margin). It should be noted that, unlike the current study, the presence of centre-involving DME was not an exclusion criterion in Protocol S, and a total of 53% of eyes in the PRP group of Protocol S received additional ranibizumab injections during the 24-month follow-up.

In the Protocol S study, ranibizumab resulted in visual acuity gains of +2.8 letters compared with +0.2 letters gained in the PRP treatment group at 2 years. Among eyes without DME at baseline in Protocol S, mean change in visual acuity letter score differed by +1.4 letters between the ranibizumab and PRP groups. More recently, the 5-year follow-up data from Protocol S have been published. Similar BCVA gains were reported between the ranibizumab and PRP groups at Year 5 (3.1 and 3.0 mean letter gain from baseline, respectively). The mean change in cumulative visual field total point score favoured the ranibizumab arm (−330 dB versus −527 dB in the PRP group). Of note, while fewer eyes in the ranibizumab
The CLARITY study was a phase IIb, non-inferiority trial with 232 patients, which compared the VEGF inhibitor aflibercept versus PRP in PDR patients with respect to visual and NV outcomes (Sivaprasad et al. 2017). In CLARITY, the presence of DME was an exclusion criterion. At Month 12, there was a +3.9 letter difference between patients randomized to aflibercept versus PRP-treated patients, in favour of aflibercept ($p < 0.0001$). Patients in CLARITY receiving aflibercept showed significantly greater regression of NV compared with PRP-treated patients ($p < 0.0001$). In addition, there was also a significant difference in patient satisfaction scores, with PDR patients preferring anti-VEGF therapy to PRP therapy, at least in a clinical trial setting and over a limited period of time (Sivaprasad et al. 2017).

In contrast to the original ETDRS severity scale grading, multimodal imaging including FA in addition to colour fundus photography was used in our study for the detection of NVs, and a modified 8-field protocol using wide-field images was applied. As small areas of NV may be easier to detect using FA compared with colour fundus photography and a larger area of the fundus is captured using our modified protocol, this may result in a higher number of eyes staged as PDR compared with a purely colour fundus photography-based assessment using $30^\circ$ images. Furthermore, PRP treatment was not considered a criterion for PDR staging for the PRIDE study. Therefore, severity levels could decrease from PDR to NPDR even in the PRP group if complete regression of leakage from NV was not achieved.

**Fig. 4.** Fluorescein angiography composites.

**Fig. 5.** Non-proliferative and proliferative diabetic retinopathy. Please note that two patients in the combination group had a vitrectomy prior to Month 12 due to retinal detachment or vitreous haemorrhage. However, these two patients are not shown as high-risk or advanced PDR in this figure because their last visit prior to vitrectomy did not include fluorescein angiography assessment. ETDRS: early treatment diabetic retinopathy study; NPDR: Non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; PRP: panretinal laser photoocoagulation.
detected as well as the absence of fibrous proliferations. It is noteworthy that about 50% of patients in the ranibizumab groups were staged as NPDR at Month 3, and about two-thirds of these demonstrated complete regression of NV leakage. It is likely that this rate was not maintained up to Month 12 due to a possible under-treatment after the initial upload. Indeed, more intensive retreatment might be advisable for these patients to stay at an NPDR level. In general, although no additive effect of combination therapy in terms of NV area reduction was seen, it may confer a benefit in terms of lowering the risk of development of high-risk PDR. When looking at the ETDRS severity scale at Month 12, fewer patients showed high-risk PDR and more patients had mild PDR in the combination group compared with patients treated with ranibizumab alone or PRP. This is an important finding as there is a greater risk of bleeding in eyes with high-risk PDR (ETDRS 1991c; Brucker et al. 2009). In this study, none of the patients in the ranibizumab group but two patients in the PRP group and three patients in the combination group required vitrectomy.

At Month 12, the number of patients with PDR levels equalizes between groups owing to NV recurrences as well as development of new NVs in the ranibizumab groups. Although the number of patients who developed new NVs up to Month 12 was comparable between all groups, patients in the PRP group already demonstrated new NVs at Month 3, whereas in the ranibizumab groups only one patient developed new NV. It needs to be evaluated whether occurrence of new NVs may be prevented more effectively with a more intense treatment regimen.

A recent meta-analysis reported that there is 'high-quality evidence' supporting a beneficial effect of anti-VEGF therapy when used in conjuction with PRP (Simunovic & Maberley 2015). However, findings from Protocol S, CLARITY and now PRIDE suggest that anti-VEGF monotherapy may be sufficient for the treatment of PDR at least over a limited time period (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015; Sivaprasad et al. 2017).

By replacing, or complementing, PRP therapy with anti-VEGF therapy, it may be possible to lessen the risk of DME associated with laser treatment, as was observed in Protocol S (Writing Committee for the Diabetic Retinopathy Clinical Research Network 2015). A similar observation was made in the current study with an increase in CST in the two laser groups only. However, it is important to be mindful of the limitations of the current study. Regarding study duration, a longer follow-up is required to fully elucidate whether additional PRP is beneficial in terms of morphological and functional outcomes. The 24-month extension of the PRIDE study will provide further insight into the durability of ranibizumab monotherapy in PDR, a possible beneficial effect of combination therapy, as well as patient compliance to intravitreal anti-VEGF injections over an extended time period. Additionally, the relatively small number of patients in PRIDE may affect the representativeness

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**Table 4. APTC events up to Month 12.**

| Safety set, n (%) | Ranibizumab 0.5 mg (n = 35) | PRP (n = 35) | Combination (n = 36) | p-value (fishers exact test) |
|------------------|-----------------------------|--------------|---------------------|----------------------------|
| APTC events      |                             |              |                     |                            |
| Cardiovascular, haemorrhagic & unknown death | 3 (8.6) | 1 (2.9) | 4 (11.1) | 0.5268 |
| Cardiogenic shock | 1 (2.9) | 1 (2.9) | 2 (5.6) | 1.0000 |
| Fatal myocardial infarction | – | – | 1 (2.8) | 1.0000 |
| Non-fatal cardiovascular, haemorrhagic events | 1 (2.9) | – | 2 (5.6) | 0.5428 |
| Non-fatal myocardial infarction | 1 (2.9) | – | – | 0.6604 |
| Non-fatal cerebrovascular accident | 1 (2.9) | – | 2 (5.6) | 0.7714 |

APTC = Anti-Platelet Trialists Collaboration. PRP = panretinal photocoagulation.

1Event occurred approximately 9 months after last ranibizumab treatment.

2One event occurred approximately 6 months after the last treatment with ranibizumab; the second event was a suspected stroke/cerebrovascular accident that led to hospitalization for medical evaluation but the suspected stroke was not confirmed. Study treatment was not stopped for this patient.
of our findings. And finally, it should also be noted that the decision to retreat was taken at the investigator’s discretion and may therefore potentially be open to subjective bias.

In conclusion, our findings indicate that ranibizumab is more effective compared with PRP monotherapy in decreasing NV area over a 12-month period and improving visual outcomes in PDR, even in patients without DME. Long-term follow-up is warranted to investigate patient adherence to anti-VEGF therapy over a longer period of time and to evaluate the recurrence rates of NV under ranibizumab monotherapy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Reasons for patient dropout during study period by treatment group.

Table S2. Change of ETDRS severity scale (shift from baseline to Month 3/Month 12), n (%).

Table S3. Vitrectomies and key ocular serious adverse events (SAEs) (as reported by the investigator).

Table S4. Key ocular adverse events up to Month 12 as reported by the investigator.

Table S5. Key non-ocular serious adverse events up to Month 12.