Observational outcomes in proliferative diabetic retinopathy patients following treatment with ranibizumab, panretinal laser photocoagulation or combination therapy – The non-interventional second year follow-up to the PRIDE study

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ABSTRACT.

Purpose: Ranibizumab monotherapy showed stronger effects on area of retinal neovascularization (NV) reduction while offering better visual acuity (VA) results than panretinal laser photocoagulation (PRP) monotherapy during the first 12 months of the PRIDE study. The second year of PRIDE was an observational, non-interventional follow-up, performed to evaluate long-term anatomical and functional outcomes in proliferative diabetic retinopathy (PDR) patients under real-life conditions, prior to the approval of ranibizumab for PDR.

Methods: Seventy-three PDR patients (28 from the ranibizumab group; 20 from the PRP group; 25 from the combination group) were included in the observational follow-up phase and treated at the investigators discretion. Visual acuity (VA) measurements and retinal imaging were performed at Months 12, 18 and 24.

Results: Mean (± SD) NV area in the ranibizumab monotherapy and combination follow-up groups increased from 3.16 ± 4.30 mm² and 1.13 ± 2.78 mm² at Month 12 to 6.09 ± 10.79 mm² and 2.14 ± 4.41 mm² at Month 18 and 10.00 ± 17.63 mm² and 3.26 ± 7.05 mm² at Month 24, respectively. In the PRP follow-up group, NV area declined from 5.44 ± 14.55 mm² at Month 12 to 1.22 ± 1.67 mm² at Month 18, but increased again to 4.05 ± 11.66 mm² at Month 24. During the observational phase, only 2 (6;8) patients in the ranibizumab (PRP;combination) follow-up group were treated with anti-VEGF medications, while 17 (6;10) patients received PRP laser therapy.

Conclusion: Discontinuation of ranibizumab treatment in PDR patients may result in an increase of NV area and VA loss. Tight monitoring of disease activity and continued treatment beyond the first year is needed to maintain disease control.

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

Introduction

Diabetic eye disease is a common cause of severe vision loss among diabetic patients (Lee, Wong, & Sabanayagam, 2015). Of the 422 million adult diabetic patients globally (WHO, 2016), it is estimated that one quarter have some form of diabetic retinopathy, and prevalence estimates of severe disease (i.e. requiring treatment) such as proliferative diabetic retinopathy (PDR) ranges from approximately 2.2% in Europe (Li et al., 2020) to approximately 6.8% globally (Yau et al., 2012). The natural history of the disease suggests that its development is primarily related to progressive retinal ischaemia arising from diabetic retinopathy (Danis & Davis, 2008). Without treatment, approximately 50% of eyes that develop PDR will experience profound vision loss within a 5-year period (DRS, 1976, DRS Research Group, 1981).

Panretinal laser photocoagulation (PRP) had been the standard of care for PDR for more than 40 years (ETDRS RG, 1991a). Panretinal laser photocoagulation (PRP) destroys areas of retinal ischaemia peripheral to the
macula in an effort to reduce oxygen demand, prevent disease progression and preserve central vision (DRS, 1976; ETDRS RG, 1991a). Panretinal laser photocoagulation (PRP), however, may be associated with a number of side-effects, including pain, transient blurring of vision, loss of peripheral or night vision, increased risk of macular oedema and central vision loss (Aiello et al., 1994).

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy such as ranibizumab has been shown to effectively and safely cause regression of neovascularization in PDR (Salam, Mathew, & Sivaprasad, 2011). Studies have demonstrated that visual acuity (VA) can be improved in patients with PDR via treatment with repeated injections of anti-VEGF (Kim & D’Amore, 2012). In the Protocol S study, investigators evaluated the efficacy and safety of ranibizumab versus PRP over 5 years in PDR patients (baseline DME was not an exclusion criterion). Both treatments achieved good VA at 5 years (mean gain of ~3 letters in each group) (Gross et al., 2018). In a small ($n = 35$), 12-month, randomized controlled trial of high-risk PDR patients, Figueira et al. (2016) reported that a combination of intravitreal anti-VEGF therapy and PRP might offer additional efficacy in the regression of retinal NVs versus either treatment alone.

The PRIDE study was designed to compare ranibizumab, PRP and a combination of both therapies in terms of their impact on NV in PDR patients without DME (Lang et al., 2020). Analysis of the primary endpoint revealed that ranibizumab monotherapy was significantly more effective than PRP in reducing the area of NV between baseline and Month 12 in patients with PDR. More patients in the ranibizumab and combination groups showed complete regression of leakage from NVs compared to patients in the PRP group. Furthermore, ranibizumab monotherapy led to significantly better outcomes in best-corrected visual acuity (BCVA) and central subfield thickness (CST) in comparison to PRP monotherapy.

After the 12-month core phase of the PRIDE study, patients were followed up in an observational (non-interventional) manner until Month 24. Treatment during this phase was performed at the discretion of the investigator and no study medication was provided. The PRIDE study was conducted between 2012 and 2017 at a time when no anti-VEGF therapy was approved for treatment of PDR in the European Union (EU). Here, we present the results from this observational second year follow-up phase of the PRIDE study.

### Methods

The PRIDE study (NCT01594281) is a phase II, 12-month, randomized (1:1:1), open-label, but reading centre masked, controlled, multicentre study with an observational follow-up phase until Month 24 evaluating ranibizumab versus PRP versus a combination of both therapies in PDR patients without DME. In total, 106 patients with PDR were included in the interventional core phase (baseline to Month 12) (full analysis set [FAS]) and randomized (1:1:1) as follows: ranibizumab 0.5 mg ($n = 35$), PRP ($n = 35$) and combination (ranibizumab 0.5 mg + PRP) ($n = 36$). Inclusion and exclusion

![Fig. 1. Patient disposition during the study. BL = baseline, FU = follow-up, ICF = informed consent form. Note: only patients who signed a new ICF could be included in the follow-up phase. *One of the two patients that were lost to follow-up in the PRP follow-up group withdrew without documented data in the follow-up and, thus, was not included in the FUS, which consisted of 73 patients.](image)
criteria have been described previously (Lang et al., 2020). A total of 73 patients with PDR (28 patients of the former ranibizumab 0.5 mg group; 20 patients of the former PRP group; 25 patients of the former combination group) were included in the observational follow-up phase (Month 12–24) (follow-up set [FUS]). For participation in the observational follow-up phase, patients had to sign an additional informed consent. No study medication was provided and patients were treated at the investigators discretion, that is independently of treatment assignment in the core phase.

Study endpoints and outcomes from the interventional first year of the PRIDE study have been reported previously (Lang et al., 2020). At Month 18 and 24, two observational study visits were performed to assess further outcomes beyond the core study period.

Details regarding efficacy assessments, including image analysis, have been described previously (Lang et al., 2020). In brief, the area of NV (neovascularization elsewhere [NVE] plus neovascularization of the disc [NVD]) was determined with early frame fluorescein angiograms. Central subfield thickness (CST) and further anatomic outcomes were assessed on spectral-domain optical coherence tomography (SD-OCT) and colour fundus photography (CFP). Fluorescein angiography (FA) and fundus photography images were captured using an 8-field protocol (modified from the ETDRS 7 standard fields [ETDRS RG, 1991b]). The same imaging system had to be used for every visit of a patient during the course of the study. 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. The graders were masked to treatment assignment. Grading reproducibility was tested by re-grading of 37 visits of nine randomly selected cases of the PRIDE study. For qualitative FA assessments, statistical analysis was performed by calculation of percentual agreement between answers. For quantitative FA analysis of area of NV, the median absolute difference between original and reproducibility grading was calculated, and the mean absolute deviation from the median. Best-corrected visual acuity (BCVA) was assessed using the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score. Any treatments required in the follow-up phase as well as adverse events were also recorded.

For both the interventional core phase and the observational follow-up phase, differences in LS (least square) means and their 2-sided 95% confidence interval (CI) were estimated with an ANCOVA model with factor treatment and covariate baseline value using the relevant population (FAS or FUS).

### Results

Patient disposition during the core phase and the observational follow-up phase is outlined in Fig. 1. Seventy-four patients entered the follow-up phase is outlined in Fig. 1. Seventy-four patients entered the follow-up phase (FUS).

| Medical condition | Ranibizumab group | PRP group | Combination group |
|-------------------|-------------------|-----------|-------------------|
| DME               | 1 (3.6%)          | 0 (0.0%)  | 0 (0.0%)          |
| Haemorrhage       | 1 (3.6%)          | 0 (0.0%)  | 0 (0.0%)          |
| PDR               | 17 (60.7%)        | 5 (25.0%) | 9 (36.0%)         |
| Total number of injections, number of patients | 3 (10.7%) | 2 (10.0%) | 4 (16.0%) |

Table 1. Treatments during the observational follow-up phase (second year).

| Observational follow-up phase (FUS) | Ranibizumab group | PRP group | Combination group |
|-------------------------------------|-------------------|-----------|-------------------|
| Number of patients who received panretinal laser therapies (at investigator’s discretion) | 17 (60.7%) | 6 (30.0%) | 10 (40.0%) |
| Reason for panretinal laser therapy, number of patients | DME | Haemorrhage | PDR |
| DME | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Haemorrhage | 0 (0.0%) | 1 (5.0%) | 0 (0.0%) |
| PDR | 17 (60.7%) | 5 (25.0%) | 9 (36.0%) |
| Mean (SD) duration between last panretinal laser therapy and last study visit in the follow-up phase, days | 274 days | 0 (0.0%) | 1 (5.0%) | 2 (8.0%) |
| Number of patients who received focal and/or grid laser therapies (at investigator’s discretion) | 3 (10.7%) | 2 (10.0%) | 4 (16.0%) |
| Number of patients who received anti-VEGF medications (at investigator’s discretion) | 2 (7.1%) | 6 (30.0%) | 8 (32.0%) |

For two patients in the ranibizumab follow-up group, panretinal laser therapies were documented as PRP rescue treatment. Please note, that these are included in this table.

Mean number of laser burns was calculated for patients in the FUS population with at least one panretinal laser therapy in the follow-up phase.

For two patients in the combination follow-up group who received one panretinal laser therapy in the follow-up phase, the number of laser burns was not documented. Therefore, the mean (SD) number of laser burns in the combination follow-up group refers to n = 8 patients with panretinal laser therapies.

Mean duration between the last panretinal laser therapy or the last injection and the last study visit was calculated for patients in the FUS population with at least one panretinal laser therapy or anti-VEGF injection in the follow-up phase, respectively.
phase (28 patients in the ranibizumab follow-up group, 21 patients in the PRP follow-up group and 25 patients in the combination follow-up group). Sixty-seven patients completed their Month 24 visit (25 patients in the ranibizumab follow-up group, 19 patients in the PRP follow-up group and 23 patients in the combination follow-up group). The disposition of patients who discontinued the follow-up phase prematurely was given as: three patients in the ranibizumab follow-up group (one patient withdrew consent, two patients were lost to follow-up), two patients in the PRP follow-up group (both lost to follow-up) and two patients in the combination follow-up group (one patient withdrew consent and one was lost due to an administrative issue).

Baseline characteristics of those who continued the observational follow-up phase of the study are detailed in Table S1. Baseline characteristics were largely well-balanced with the exception of mean (± SD) area of NV which was higher in the ranibizumab follow-up group (9.02 ± 14.63 mm²) compared with the PRP and the combination follow-up groups (6.19 ± 12.29 mm² and 2.71 ± 4.09 mm², respectively). Also, the proportion of active smokers was higher in the combination follow-up group (36.0% compared with 14.3% in the ranibizumab follow-up group and 10.0% in the PRP follow-up group).

Treatment

Study treatments in the core phase of the study have been described previously (Lang et al., 2020). Study treatments in the observational follow-up phase are outlined in Table 1. During the observational follow-up phase, no study medication was provided and patients were treated at the discretion of the investigator (i.e. treatment was independent of treatment assignment in the core phase and any anti-VEGF therapy as well as laser treatment could be used).

Area of neovascularization

In the interventional first year (FAS population), ranibizumab monotherapy led to significantly greater reduction in NV area from baseline to Month 12 compared with PRP (p = 0.0344), while comparison between ranibizumab and combination therapy was non-significant, as was the comparison between PRP and combination therapy (Lang et al., 2020).

In the observational follow-up phase (FUS population), mean (± SD) NV area in the ranibizumab follow-up group increased from 3.16 ± 4.30 mm² at Month 12 to 6.09 ± 10.79 mm² at Month 18 and 10.00 ± 17.63 mm² at Month 24. In the PRP follow-up group, NV area declined from 5.44 ± 14.55 mm² at Month 12 to 1.22 ± 1.67 mm² at Month 18, but increased again to 4.05 ± 11.66 mm² at Month 24. In the combination follow-up group, NV area increased from 1.13 ± 2.78 mm² at Month 12 to

![Fig. 2. Fluorescein angiography over 24 months follow-up of a patient randomized to the ranibizumab group in the interventional core phase, who received no further injections during the observational follow-up phase. (A) early phase fluorescein angiogram (FA), (B) magnified section from white rectangle in A, (C) late phase FA. At Month 3, leakage from neovascularization of the disc (NVD) and neovascularization elsewhere (NVE) regressed completely. At Month 12, leakage recurred despite a total of 6 intravitreal anti-VEGF injections given with the last injection 3 months prior to the Month 12 visit. During the observational follow-up phase, no further injections were performed and a severe increase in NVE and NVD area was detected despite panretinal laser therapy (905 laser burns between Month 12 and Month 18 and 787 laser burns between Month 18 and Month 24). Note that at Month 12, there seemed to be reperfusion within a small area of nonperfusion detected at the screening visit (SCN) (white arrow in B), however, a new NVD developed in this area up to Month 24.]
2.14 ± 4.41 mm² at Month 18 and 3.26 ± 7.05 mm² at Month 24. The LS mean change (95% CI) in NV area from baseline to Month 24 in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group was 1.0 (−3.2; 5.1) mm², −2.2 (−6.9; 2.5) mm² and −0.6 (−5.2; 3.9) mm², respectively (Figs 2–4). The differences between groups were non-significant. Analysis was adjusted for baseline NV area (ANCOVA).

The number of patients developing new NVE compared to baseline (i.e. new NVE that were not observed at baseline) in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group was 7 (25.9%), 5 (25.0%) and 6 (24.0%) at Month 12, 10 (37.0%), 5 (26.3%) and 10 (41.7%) in the observational phase at Month 18, and 10 (40.0%), 8 (42.1%) and 12 (54.5%) at Month 24, respectively (Table 2). The number of patients who developed new NVD compared to baseline in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group was 1 (3.7%), 0 (0.0%) and 1 (4.0%) at Month 12, 4 (14.8%), 0 (0.0%) and 2 (8.3%) at Month 18, and 2 (8.0%), 0 (0.0%) and 1 (4.5%) at Month 24, respectively (Table 2).

Data on blocked fluorescence (BF) potentially obscuring NV on FA at each study visit are outlined in Table 2.

The number of patients who experienced complete regression of NV leakage in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group was 6 (22.2%), 2 (10.0%) and 5 (20.0%) at Month 12, 3 (11.1%), 4 (21.1%) and 4 (16.7%) in the observational follow-up at Month 18, and 3 (12.0%), 4 (23.5%) and 5 (22.7%) at Month 24, respectively (Fig. 5).

With respect to grading reproducibility, the percental agreement for evidence of NVE on FA was 94.6% and for evidence of NVD was 100%. The median difference (±mean absolute deviation) between gradings for area of NVE was 0.11 mm² (±0.12 mm²) (range: 0.00–10.98 mm²), with a median value (±mean absolute deviation) of original grading of 0.52 mm² (±6.65 mm²) (range: 0.00 mm²–57.19 mm²). For area of NVD, the median difference (±mean absolute deviation) between gradings was 0.00 mm² (±0.14 mm²) (range: 0.00 mm²–1.8 mm²), with a median value (±mean absolute deviation) of original grading of 0.00 mm² (±0.23 mm²) (range: 0.00 mm²–3.22 mm²).

In the observational follow-up phase, mean (± SD) BCVA in the ranibizumab follow-up group decreased from 85.6 ± 7.6 letters at Month 12 to 81.9 ± 10.8 letters at Month 18 before increasing marginally to 82.4 ± 9.9 letters at Month 24. In
the PRP follow-up group, mean (± SD) BCVA decreased from 78.0 ± 14.8 letters at Month 12 to 77.2 ± 19.6 letters at Month 18 before increasing to 78.7 ± 16.7 letters at Month 24. In the combination follow-up group, mean (± SD) BCVA increased from 81.4 ± 9.3 letters at Month 12 to 82.5 ± 6.9 letters at Month 18, before declining to 78.5 ± 18.3 letters at Month 24. The LS mean (95% CI) change in BCVA from baseline to Month 24 in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group was −1.1 (−6.7; 4.6) letters, −2.0 (−8.5; 4.5) letters and −4.2 (−10.1; 1.6) letters, respectively (Fig. 6). The differences between groups were non-significant.

![Graph showing changes in BCVA](image)

**Fig. 4.** Change in area of neovascularization (NVE + NVD) from baseline to Month 24 (FUS). Differences in LS (least square) means and their 2-sided 95% CIs are estimated with an ANCOVA model with factor treatment and covariate baseline value using the FUS population. Missing values were not replaced. Treatment differences between groups were non-significant at Month 24: Ranibizumab - Panretinal Laser: p = 0.3131; Ranibizumab – Combination: p = 0.6149; Panretinal Laser – Combination: p = 0.6223. FUS = Follow-up set, NV = neovascularization, NVD = neovascularization of the disc, NVE = neovascularization elsewhere, PRP = panretinal laser photocoagulation.

| Table 2. Morphological and visual outcomes. |
|--------------------------------------------|
| **FUS population**                          |
| Ranibizumab follow-up group n = 28          |
| PRP follow-up group n = 20                  |
| Combination follow-up group n = 25          |
| Change in sum of NV area (NVD and NVE) (mm²), mean (SD) | |
| Month 12 (interventional)                   |
| −5.9 (12.9)                                |
| −3.2 (9.0)                                 |
| −0.0 (15.9)                                |
| Month 18 (observational)                    |
| −5.8 (12.9)                                |
| −4.5 (13.0)                                |
| −2.1 (3.0)                                 |
| Month 24 (observational)                    |
| −1.6 (3.1)                                 |
| −0.7 (4.9)                                 |
| −0.4 (6.7)                                 |
| Number of patients with development of new NVE compared to baseline by visit and treatment |
| Month 12 (interventional)                   |
| 7 (25.9%)                                  |
| 10 (40.0%)                                 |
| 12 (42.8%)                                 |
| Month 18 (observational)                    |
| 5 (25.0%)                                  |
| 5 (26.3%)                                  |
| 9 (45.0%)                                  |
| Month 24 (observational)                    |
| 6 (24.0%)                                  |
| 10 (41.7%)                                 |
| 15 (60.0%)                                 |
| Number of patients with development of new NVD compared to baseline at Month 12, 18 or 24 |
| Month 12 (interventional)                   |
| 7 (25.9%)                                  |
| 10 (40.0%)                                 |
| 12 (42.8%)                                 |
| Month 18 (observational)                    |
| 5 (25.0%)                                  |
| 8 (41.7%)                                  |
| 15 (60.0%)                                 |
| Month 24 (observational)                    |
| 6 (24.0%)                                  |
| 10 (41.7%)                                 |
| 15 (60.0%)                                 |
| Number of patients with blocked fluorescence (BF) potentially obscuring NV on FA by visit and treatment |
| Baseline                                   |
| 4 (14.3%)                                  |
| 14 (58.0%)                                 |
| 1 (4.0%)                                   |
| Month 12 (interventional)                   |
| 4 (14.8%)                                  |
| 10 (40.0%)                                 |
| 1 (4.0%)                                   |
| Month 18 (observational)                    |
| 4 (14.8%)                                  |
| 8 (32.0%)                                  |
| 2 (8.3%)                                   |
| Month 24 (observational)                    |
| 2 (8.0%)                                   |
| 10 (40.0%)                                 |
| 1 (4.0%)                                   |
| Change in BCVA (ETDRS letters), mean (SD)   |
| Month 12 (interventional)                   |
| 2.4 (5.3)                                  |
| −1.4 (10.4)                                |
| −1.3 (7.9)                                 |
| Month 18 (observational)                    |
| −2.3 (15.9)                                |
| −3.1 (20.7)                                |
| −1.6 (17.7)                                |
| Month 24 (observational)                    |
| −1.2 (8.7)                                 |
| −0.3 (5.7)                                 |
| −4.3 (15.4)*                               |
| Change in CST (µm), mean (SD)               |
| Month 12 (interventional)                   |
| −3.4 (15.2)                                |
| −11.6 (16.7)                               |
| 21.7 (26.6)                                |
| Month 18 (observational)                    |
| 29.2 (42.5)                                |
| 14.8 (24.6)                                |
| 15.0 (21.4)                                |
| Month 24 (observational)                    |
| 12.3 (28.4)                                |
| 12.4 (21.5)                                |
| 24.8 (17.7)                                |

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

*One of the patients in the combination follow-up group was documented with a BCVA of 68 letters at Month 18 and 0 letters and vitreous haemorrhage at Month 24.

CST

In the interventional first year (FAS), there were significant LS mean (95% CI) differences in CST change from baseline to Month 12 of −40.7 (−62.1; −19.3) µm between the ranibizumab and the PRP group (p = 0.0003) and of −22.9 (−44.2; −1.6) µm between the ranibizumab and the combination group (p = 0.0357).
There was a non-significant difference between the PRP and the combination group (PRP-combination: 17.8 [-3.7; 39.3] μm, p = 0.1034).

In the observational follow-up phase, mean (± SD) CST in the ranibizumab follow-up group at Month 12 was 237.7 ± 27.0 μm which increased to 253.2 ± 26.1 μm at Month 18 and 264.0 ± 37.5 μm at Month 24. In the PRP follow-up group, mean (± SD) CST decreased from 281.6 ± 65.3 μm at Month 12 to 269.6 ± 40.2 μm at Month 18 and 266.4 ± 41.8 μm at Month 24. In the combination follow-up group, mean (± SD) CST was 254.5 ± 37.1 μm and 254.9 ± 29.2 μm at Month 12 and Month 18, respectively, before increasing to 265.6 ± 33.4 μm at Month 24. The LS mean change (95% CI) in CST from baseline to Month 24 in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group was 21.6 (12.2; 31.0) μm, 15.5 (4.8; 26.2) μm and 24.6 (14.7; 34.4) μm, respectively (Fig. 7). The differences between groups were non-significant.

At Month 12, there were 0 (0%), 7 (37%) and 2 (9%) patients with macular oedema (defined here as CST ≥ 300 μm) in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group, respectively. In the observational follow-up phase, at Month 18, there were 1 (4%), 5 (26%) and 2 (9%) patients with macular oedema (CST ≥ 300 μm) in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group, respectively. At Month 24, there were 3 (13%), 5 (28%) and 3 (14%) patients with macular oedema (CST ≥ 300 μm) in the ranibizumab follow-up group, the PRP follow-up group and the combination follow-up group, respectively. The difference between the ranibizumab and the PRP follow-up groups was significant at Month 12 (p = 0.0009), while the other differences for CST ≥ 300 μm were non-significant.

**ETDRS severity scale**

ETDRS severity scales for patients of the FUS population are illustrated in Fig. 8. A shift table for ETDRS severity scale change between Month 12 and Month 24 can be found in Table S2.

**Safety (FUS)**

In the observational follow-up phase, no Anti-Platelet Trialists’ Collaboration (APTC) events were recorded for any of the former treatment groups.

No patients underwent a vitrectomy in either the ranibizumab and PRP follow-up groups during the non-interventional second year, while two (8%) patients required a vitrectomy in the combination follow-up group (one patient due to vitreous haemorrhage, one patient due to worsening of PDR). One (3.6%) patient experienced at least one ocular SAE in the ranibizumab follow-up group, and two patients (10.0%) and four patients (16.0%) in the PRP and combination follow-up groups, respectively (Table 3). One patient in the combination follow-up group was documented with a BCVA of 68 letters at Month 18 and 0 letters and vitreous haemorrhage at Month 24, which is not included in Table 3 as this vitreous haemorrhage was not reported as SAE by the investigator.

Key ocular AEs and non-ocular SAEs were reported in the combination follow-up group (36.0%) compared to the ranibizumab follow-up group (14.3%) and the PRP follow-up group (15.0%).

**Discussion**

In the 12-month core phase of the PRIDE study, ranibizumab monotherapy resulted in a significantly reduced NV area compared to PRP monotherapy, significantly better visual outcomes compared to PRP monotherapy and a significant reduction in CST versus PRP and combination therapy (Lang et al., 2020). Data from this second year observational follow-up of the PRIDE study facilitate further insight into the retreatment needs of PDR patients beyond the first year. To our knowledge, this is the first study in PDR where patients were switched from a controlled interventional study phase to an observational study phase allowing for the assessment of changes under real-world conditions at a time when ranibizumab was not approved for the treatment of proliferative diabetic retinopathy in the European Union (EU).

In this exploratory analysis from the second, observational year of the PRIDE study in which patients were treated at the investigator’s discretion as needed, we report that the improvements in NV area seen in the ranibizumab monotherapy group at Month 12 could not be sustained until Month 24. The NV area in the ranibizumab follow-up group increased in the second year, with NV area at Month 24 exceeding both the Month 12 and baseline values. Of note, only two patients (7.1%) in the ranibizumab follow-up group received further anti-VEGF injections during this study.
period (at the time of this study, anti-VEGF therapy, including ranibizumab, was not approved for the treatment of PDR in the EU), while 17 patients (60.7%) received PRP.

In the PRP follow-up group, NV area decreased in the second year compared to Month 12, possibly explained by a delayed effect of laser treatment performed during the first year of the study, as well as the higher number of patients receiving anti-VEGF injections in the second year for DME in this group (25.0%).

In contrast, NV area increased between Month 12 and Month 24 in the combination follow-up group, despite this group having a higher percentage of patients treated with anti-VEGF injections (32.0%) or PRP (40.0%) compared to the PRP follow-up group (30.0% each) during the second year. However, for those patients in the combination follow-up group who received treatment in the observational second year, the mean duration between the last PRP treatment as well as the last anti-VEGF injection and their last study visit was approximately 6 months. This may possibly explain the detected NV activity at this visit.

The number of patients with complete regression of NV leakage decreased in the ranibizumab follow-up group possibly due to NV recurrences arising from anti-VEGF treatment discontinuation and increased in the PRP follow-up group possibly because of a delayed effect of PRP treatment during the second year. While the number of patients newly developing NVD during follow-up was low in all groups, interestingly, the number of patients who developed new NVE was relatively high in all groups. These results suggest a need for continuous treatment and close monitoring of PDR beyond the first year due to the possibility of NV recurrence or development of new NV, if initial efficacy gains are to be maintained. The fact that some patients received their first retreatment with PRP or anti-VEGF more than 9 months (>274 days) after the end of the core study highlights the relevance of continuous monitoring also for those patients with absence of disease activity after the initial treatment phase.

The need for tight controls and potentially ongoing therapy in anti-VEGF treated PDR eyes is supported by findings from the five-year Protocol S study. At 2 years, visual outcomes in the ranibizumab group were non-inferior to those in the PRP group, with mean visual acuity gains of +2.8 letters in the ranibizumab
group compared to +0.2 letters in the PRP group (Writing Committee for the DRCR, 2015). Eyes in the ranibizumab group received a mean (SD) number of 7.1 (2.2), 3.3 (2.9), 3.0 (2.8), 2.9 (2.7) and 2.9 (2.8) injections during Years 1–5. With this continued anti-VEGF treatment, VA could be maintained above baseline levels and was comparable with eyes in the PRP group at 5 years (mean gain of ~3 letters in each group) (Gross et al., 2018). Additionally, lower rates of DME and visual field loss were observed in the ranibizumab group after 2 and after 5 years (Writing Committee for the DRCR, 2015; Gross et al., 2018). The importance of continued follow-up is also demonstrated in a retrospective cohort study of 76 PDR eyes by Obeid et al., (2019) in which eyes lost to follow-up for more than 6 months after anti-VEGF injection had poorer anatomic outcomes than eyes after PRP treatment. Further studies are needed to investigate the long-term treatment strategy with ranibizumab and combination therapy for patients with PDR.

Although the PRIDE study was not designed to determine optimal monitoring or treatment intervals for PDR patients, it is important to note that our observations with respect to monitoring are aligned with guidelines from various international ophthalmological societies. According to the AAO Diabetic Retinopathy Preferred Practice Pattern 2019 guidelines, 3–4 month follow-up is recommended for non-high-risk PDR without DME, 2–4 month follow-up is recommended for high-risk PDR without DME or any PDR with non-centre involving DME, while monthly follow-up is recommended for PDR with centre involving DME (AAO, 2019). The guideline for PDR therapy by the German ophthalmological societies recommends three initial monthly injections if PDR is treated with anti-VEGF, followed by further monthly injections until the NV regresses completely or is stable over three consecutive injections (‘Supplementary statement of the German Ophthalmological Society (DOG), the Retinological Society (RG) and the Professional Association of German Ophthalmologists (BVA) on treatment of proliferative diabetic retinopathy : Status November 2019’, 2020). It recommends monthly control visits for at least three months after the last injection before control intervals can be extended. After panretinal laser therapy for PDR with no macular oedema, the first control visit should occur after 3 months, thereafter the interval can be extended.

Changes in BCVA and CST outcomes in the PRIDE study followed a similar trend in the second year. The improvements in BCVA and CST with ranibizumab monotherapy from the first 12 months could not be sustained during the observational phase until Month 24. Mean BCVA decreased from Month 12 to Month 18, then remained stable until Month 24, while CST increased during the second year. In the PRP follow-up group, CST and BCVA slightly improved in the second year compared to Month 12, again possibly indicating a delayed effect of PRP treatment. In the combination follow-up group, CST increased while BCVA decreased at Month 24 compared with Month 12. Of note, the number of patients with DME at Month 24 (defined as CST ≥ 300 µm) was highest in the PRP follow-up group (28%) compared to the ranibizumab follow-up group (13%) and the combination follow-up group (14%), respectively, underlining the beneficial effect of anti-VEGF treatment on DME development.

Looking at the ETDRS severity scale at Month 24, the number of patients classified as NPDR declined in the ranibizumab follow-up group compared to Month 12. This finding is

**Table 3.** Vitrectomies and ocular serious adverse events (SAEs) in the observational follow-up phase (as reported by the investigator).

| Preferred term, n (%) | Safety set | Ranibizumab follow-up group n = 28 | PRP follow-up group n = 20 | Combination follow-up group n = 25 |
|-----------------------|------------|------------------------------------|----------------------------|-----------------------------------|
| Safety set            |            | n = 28                            | n = 20                     | n = 25                            |
| Vitrectomy            |            | -                                 | -                          | 2 (8.0%)                          |
| Total number of patients with at least 1 SAE |            | 1 (3.6%)                          | 2 (10.0%)                  | 4 (16.0%)                          |
| Diabetic retinopathy  |            | -                                 | -                          | 2 (10.0%)                          |
| Retinal haemorrhage   |            | 1 (3.6%)                          | -                          | -                                 |
| Vitreous haemorrhage  |            | -                                 | -                          | 1 (4.0%)                          |

Fig. 8. Non-proliferative and proliferative diabetic retinopathy (FUS). PRP treatment was not considered for staging, thus eyes with neither NV leakage nor fibrous proliferation could receive NPDR staging during follow-up. FUS = follow-up set, NV = neovascularization, NPDR = non-proliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, PRP = panretinal laser photocoagulation.
likely attributable to under-treatment observed in these patients after the end of the interventional core study. At Year 5 in the Protocol S study, for example, in which eyes in the ranibizumab group received an average of three injections per year between Years 2–5, 46% of eyes showed an improvement of ≥2 steps in DR severity compared to baseline, with 33% improving from PDR to NPDR at Year 5 (Gross et al., 2018). Of note, a small increase in patients classified as NPDR was observed in the combination follow-up group. The percentage of patients with high-risk PDR showed a decline until Month 18 and remained stable until Month 24 in the PRP follow-up group, while it remained relatively stable in the ranibizumab follow-up group during the second year. Rates of high-risk PDR declined from baseline to Month 12 in the combination group but increased again to baseline levels during the observational phase until Month 24. Multimodal imaging including FA in addition to CFP and a modified 8-field protocol using wide-field images were used for the detection of NVs. The data showed that the sensitivity for detection of NV was higher on FA compared to CFP. Of 69 patients with evidence of NVE and 21 patients with evidence of NVD on FA at baseline, only 41 and 16 were also detected on CFP, respectively. As small areas of NV are easier to detect using FA compared with CFP and a larger area of the fundus was captured using the modified protocol, this may have resulted in a higher number of patients staged as PDR compared with other studies using a purely CFP-based assessment and 30° images.

A key strength of this study is the observational nature of the second year. This observational phase allows the opportunity to study the long-term effects in a real-world setting of prior interventions in PDR patients. In doing so, it is possible to highlight limitations of the PDR treatment paradigm, such as the deleterious effects of anti-VEGF under-treatment in these patients. It must be noted that ranibizumab was not approved for use in PDR in the EU at the time of the study. In the interpretation of these results, it should also be noted that the numbers of patients in each of the follow-up groups were relatively small and results should not be generalized without caution.

In conclusion, our data from the observational second year 12-month follow-up of the PRIDE study indicate that PDR patients require regular monitoring of disease activity. For patients receiving anti-VEGF therapy, continuous treatment is important to ensure that the benefits are not lost due to recurrent NV activity.

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Supporting Information

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

**Table S1** Baseline patient characteristics for the follow-up set, by treatment group.

**Table S2** Change of ETDRS severity scale* (shift from Month 12 to Month 24), n (%)a,b

**Table S3** Key ocular adverse events in the observational follow-up phase (as reported by the investigator)*

**Table S4** Key nonocular serious adverse events in the observational follow-up phase.