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Agnès Glacet-Bernard, Jean-François Girmens, Laurent Kodjikian, Cécile Delcourt, Franck Fajnkuchen, Catherine Creuzot-Garcher, Pascale Massin, Nathalie San Nicolas

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**Real-world outcomes of ranibizumab treatment in French patients with visual impairment due to Macular Edema secondary to Retinal Vein Occlusion: 24-month results from the BOREAL-RVO study.**

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**Short Title:** Real-world 24-month study of ranibizumab for RVO (BOREAL-RVO)

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## **Abstract**

### **Introduction**

Information about real-world ranibizumab use is needed to optimize treatment of macular edema secondary to retinal vein occlusion (RVO). The BOREAL-RVO study assessed treatment use, effectiveness and safety of 24-month treatment with ranibizumab 0.5 mg in patients with visual impairment due to macular edema secondary to RVO in a real-world setting.

### **Methods**

This was a multicenter, post-authorization, observational study in France, including patients starting ranibizumab for RVO. Primary endpoint was mean change from baseline in best-corrected visual acuity (BCVA) at Month 6. Secondary endpoints were mean changes from baseline in BCVA at Month 24 and central retinal thickness (CRT) at Months 6 and 24, and treatment use in real-world setting.

### **Results**

226 branch RVO (BRVO) and 196 central RVO (CRVO) patients were enrolled; 71.7% and 70.9% completed the 24-month follow-up, respectively. In BRVO, mean (SD) baseline BCVA was 55.2 (18.7) letters, with gains of 14.3 (13.7), 14.1 (16.5), 13.0 (17.5) and 11.4 (20.1) letters at Months 3, 6, 12 and 24. In CRVO, mean (SD) baseline BCVA was 40.4 (25.6) letters, with gains of 16.0 (21.2), 9.5 (25.4), 9.2 (27.7) and 8.3 (23.8) letters at Months 3, 6, 12 and 24. At Month 24, 52% of BRVO and 41% of CRVO patients had gains of 15 or more letters. In BRVO, mean (SD) CRT values at baseline and Months 3, 6, 12 and 24 were 550 (175), 315 (104), 343 (122), 335 (137) and 340 (105)  $\mu\text{m}$ . In CRVO, mean (SD) CRT values at baseline and Months 3, 6, 12 and 24 were 643 (217), 327 (152), 400 (203), 379 (175) and 348 (161)  $\mu\text{m}$ . On average, BRVO patients had 3.8 injections for 6.9 visits by Month 6, and 7.2 injections for 19.7 visits by Month 24. CRVO patients had 2.7 injections for 4.2 visits by Month 6, and 7.1 injections for 21.1 visits by Month 24. Factors predictive of better BCVA gain at Month 6 were age under 60 at baseline, lower baseline BCVA and BCVA gain at Month 3. There were no new safety findings.

### **Conclusion**

Major improvements in BCVA and CRT were observed at Month 3 after the induction phase, and then was sustained up to Month 24, with a slight decrease, probably due to under-treatment. This study demonstrated ranibizumab to be a safe and effective treatment for BRVO and CRVO in the real-world setting, although more regular or pro-active treatment could further improve outcomes.

## **Introduction**

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy and can lead to poor visual outcomes [1]. The most common type is branch RVO (BRVO), followed by central RVO (CRVO) and hemi-occlusion of the central retinal vein (HRVO) [1, 2]. BRVO and CRVO global prevalence in 2015 was estimated at 0.64% and 0.13% respectively [3]. The main risk factors for any RVO include older age, hypertension, glaucoma, history of heart attack or stroke, hyperlipidemia, and obstructive sleep apnea [3-5].

Ranibizumab is a humanized monoclonal anti-vascular endothelial growth factor (anti-VEGF) antibody fragment that inhibits the effects of VEGF on neovascularization, angiogenesis and vascular permeability. Ranibizumab was approved in Europe in 2011 for treating visual impairment due to macular edema (ME) secondary to RVO [6], based on data from the phase 3 randomized clinical trials (RCTs) CRUISE and BRAVO [7, 8].

However, results from RCTs may not reflect effectiveness in the real-world setting, where real-life practices may differ from the strictly controlled conditions of the RCTs. Post-authorization studies provide important information about how medicines are used in routine clinical practice, and how effective they are. This study was mandated by the French Transparency Commission during the approval of ranibizumab reimbursement for RVO and diabetic macular edema, with the aim of providing data on the effectiveness, safety and follow-up in a real-life setting. Here, we report the results from the BOREAL-RVO real-world observational study that evaluated the change in best corrected visual acuity up to 24 months in patient starting treatment with ranibizumab for decreased vision due to ME secondary to RVO.

## **Methods**

### **Study design**

This prospective multicenter observational study was conducted to assess real-world use and effectiveness of ranibizumab in patients with ME secondary to 1) CRVO and 2) BRVO/HRVO (called the BRVO group hereafter, for ease of reading). By decision of the Scientific Committee and similarly to BRAVO [8], HRVO patients were included in the BRVO group as the treatment of macular edema for both entities is similar and may include grid laser photocoagulation. The study was conducted in France between December 2013 and April 2015, following approval from the French agencies for data protection (CNIL) and health research data management (CCTIRS). This study was conducted in accordance with the tenets of the Declaration of Helsinki. Participating patients were informed about the study and signed informed consent forms.

### **Selection of investigators**

One thousand six hundred sixty-six French retina specialists from both private practice and public hospitals were invited to participate, with the expectation that 150 would accept and that 120 would enroll patients. Each participating ophthalmologist had 16 months to enroll a maximum of 16 patients each.

### **Inclusion/exclusion criteria**

Eligible patients were consenting patients starting ranibizumab treatment for visual impairment due to CRVO, HRVO or BRVO, regardless of the level of initial visual acuity. Exclusion criteria were minimal, to achieve a study population representative of the larger patient population in France. Patients unwilling to participate, or who were already participating in another trial were excluded.

### **Treatment**

Patients were treated with intravitreal injection of ranibizumab 0.5 mg, according to prescribing information. Following ranibizumab initiation, patients were re-treated as needed according to the ophthalmologist's decisions based on anatomic and functional criteria.

## Data collection

Data were collected from patients' medical records at baseline and at Months 3, 6, 9, 12, 18 and 24. Data were also collected via telephone interviews at baseline and at Months 12 and 24. Detailed information was collected at baseline regarding patient characteristics, medical history, prior and concomitant medications.

Ophthalmologists measured patient BCVA according to their standard practice. BCVA data provided using the Snellen or Monoyer scales were converted to the Early Treatment Diabetic Retinopathy Study (ETDRS) scale using standard conversion tables. Central retinal thickness (CRT) was measured using optical coherence tomography (OCT) on central ETDRS subfield. Adverse events (AEs) were recorded at each visit. Fluorescein angiography was performed according to the ophthalmologist's routine practice and ischemic RVO was defined as the presence of retinal non-perfusion of 10-disc areas or more.

Patients were monitored and treated according to the ophthalmologist's routine practice. Investigating ophthalmologists retreated patients at their discretion and could switch treatment.

## Statistical analysis

The primary outcome measure was the change from baseline in BCVA at Month 6 according to the ETDRS scale. Analyses were performed using SAS software version 9.3.

Based on previous RCTs evaluating ranibizumab in ME secondary to RVO [7, 8], a sample size of 285 patients allowed a relative precision of 10% relative to the average BCVA. Assuming potential attrition of 10%, it was planned to recruit 320 BRVO patients and 320 CRVO patients.

Quantitative variables were described using mean, standard deviation, median and extreme values, as well as 2-sided 95% confidence intervals. Qualitative variables were described as absolute frequency and percentage. Sub-group analyses were performed according to various baseline disease characteristics and demographics. Safety was assessed at Month 24 for all patients who received at least one ranibizumab injection.

Multivariate linear regression was used to identify potential predictive factors of BCVA improvement at Month 6 and 24 and included patients followed and with BCVA measurements at these timepoints. Explanatory variables included baseline demographic and disease characteristics as well as treatment modalities and response. Variables that were significant in a univariate analysis (at the 20% threshold) were included in the multivariate analysis.

## Results

Of the 1,666 ophthalmologists invited to participate in the study, 236 (14.2%) accepted, 82 (4.9%) included at least 1 BRVO patient, and 79 (4.7%) included at least 1 CRVO patient. The most common reason for non-participation of ophthalmologists was lack of time (59.4%).

### Patients and baseline characteristics

Overall, 226 patients were enrolled into the BRVO cohort (176 with BRVO, 50 with HRVO) and 196 patients were enrolled into the CRVO cohort. Follow-up at Month 24 was recorded for 71.7% of BRVO patients and 70.9% of CRVO patients (Fig. 1). Patient baseline characteristics were similar in each cohort (Table 1).

### Treatment exposure

Over the 24-month study period, patients were regularly examined, with a mean (SD) number of visits of 19.7 (7.8) and 21.1 (8.4) in the BRVO and CRVO cohorts, respectively. The mean (SD) number of intravitreal injections over the same period was 7.2 (4.3) and 7.1 (4.4) in the BRVO and CRVO cohorts, respectively (Table 2), with approximately half the injections administered in the first 6 months.

Ranibizumab treatment starts with an induction phase of one injection per month for 3 months. Administration of 3 injections in the first 3 months was reported for 79.9% of BRVO patients and 76.4% of CRVO patients.

Up to Month 24, treatment interruptions in the studied eye were noted for 85.8% of BRVO patients and 85.6% of CRVO patients. Interruption, defined as the absence of treatment at one of the visits after the induction phase, was usually temporary. It was mostly due to clinical improvement (achievement of maximum BCVA, ME resolution or ME regression; 72.6% and 79.1% in the BRVO and CRVO cohorts, respectively). The interruption was attributed to other reasons (no BCVA improvement, edema recurrence, persistent macular edema or AE) for 15.2% and 26.7% of BRVO and CRVO patients who had interruptions.

Patients who required only 3 injections during the first 3 months and who did not switch or require additional injections due favorable functional or anatomical outcomes are described as the “happy few” and represented 12.2% of CRVO patients and 13.6% of BRVO patients.

Of the 162 BRVO patients followed at Month 24, 30.2% switched treatment from ranibizumab: 15.4% switched to dexamethasone implant, 13.6% to aflibercept and 1.2% to triamcinolone (Fig. 2). Two patients (1.2%) switched back to ranibizumab after previously switching to another treatment. Of the 139 CRVO patients followed at Month 24, 37.4% switched treatment from ranibizumab; 20.9% to aflibercept, 12.2% switched to dexamethasone implant, and 4.3% to bevacizumab. None of these patients switched back to ranibizumab.

### **Visual acuity**

In both cohorts, BCVA significantly improved from baseline at all follow-up times as early as Month 3 and was sustained until Month 24.

Rapid BCVA gains from baseline were observed at Month 3 (14.3 [13.7] and 16.0 [21.2] letters in BRVO and CRVO patients, respectively). The change from baseline then stabilized over time by Month 6 (14.1 [16.5] and 9.5 [25.4] letters, respectively) with gains maintained up to Month 24 (11.4 [20.1] and 8.3 [23.8] letters, respectively) (Fig. 3 and Supplementary Table 1).

Gains from baseline to Month 6 of at least 15 letters were noted for 94 (50.3%) BRVO patients and 67 (42.7%) CRVO patients (Supplementary Table 2). Gains in BCVA were maintained up to Month 24 in both indications (Fig. 3).

At Month 6, there was a trend towards better BCVA outcomes for CRVO patients who completed the induction phase (3 monthly injections in the first 3 months, n=121), who gained 10.6 [95% CI: 5.8;15.3] letters, compared to 5.8 [95% CI: -1.5;13.0] letters for those who did not (n=34). At month 24, CRVO patients who had more than 3 intravitreal injections of ranibizumab at M6 since inclusion were more likely to experience a gain of at least 5 EDTRS letters than patients who had less than 3 injections (p=0.0064). At Month 6, BCVA gains were similar for BRVO patients who completed induction (14.0 [95% CI: 11.3;16.6] letters; n=144) and those who did not (13.8 [95% CI: 7.9;19.7] letters; n=36).

In univariate analysis, factors predictive of lower BCVA gains at Month 6 for BRVO were CRT of less than 500  $\mu\text{m}$  at baseline (p=0.0006), absence of retinal non-perfusion at baseline (p=0.0118), diabetes (p=0.0060), hypertension (p=0.0101), and longer duration of symptoms (p=0.0372). For CRVO, factors associated with loss of at least 5 EDTRS letters at 24 months from inclusion were the presence of retinal non-perfusion at baseline (p=0.0157). Other factors were not correlated with the final visual prognosis, such as gender and associated systemic treatments.

Multivariate analysis identified several factors predictive of better BCVA change from baseline to Month 6 and Month 24 for BRVO and CRVO (Supplementary Tables 3 and 4). Factors predictive of higher BCVA gains at Month 6 for both BRVO and CRVO were younger age at baseline (p=0.0270 and p= 0.0012 respectively), lower baseline BCVA (p<0.0001 and P=0.0244 respectively) and higher BCVA gain at Month 3 (p=0.0018 and p<0.0001 respectively). Factors predictive of higher BCVA gains at Month 24 for BRVO were CRT of more than 500  $\mu\text{m}$  at baseline (p=0.0160) and higher BCVA gain at Month 3 (p<0.0001). Factors predictive of higher BCVA gains at Month 24 for CRVO were age below 70 years-old at baseline (p=0.0005), higher BCVA gain at Month 3 (p=0.0018) and no switch at M6 (p=0.0061).

### **Central retinal thickness**



The pattern of changes in CRT mirror those of BCVA. CRT improved from baseline to Month 3 in both BRVO and CRVO, with improvements maintained up to Month 24 (Fig. 4 and Supplementary Table 1). The mean (SD) improvement observed after 3 months of follow-up was -232 (167)  $\mu\text{m}$  and -330 (252)  $\mu\text{m}$  in the BRVO and CRVO groups, followed by stabilization in subsequent months. By Month 24, CRT had reduced by a mean (SD) of -211 (210)  $\mu\text{m}$  and -305 (236)  $\mu\text{m}$ , respectively.

### **Other measures**

The rate of retinal non-perfusion and ophthalmologic comorbidities rose slightly during follow-up in both BRVO and CRVO patients (Table 3). At Month 24, respectively 36.4% and 34.5% of BRVO/HRVO and CRVO patients had peripheral retinal non-perfusion, 0.6% and 9.4% had rubeosis iridis, and 30.2% and 31.7% had glaucoma or ocular hypertension (Table 3). At Month 24 of follow-up, 49 CRVO patients (35.3%) had received panretinal photocoagulation (PRP) laser treatment at least once, with an average of 3.8 ( $\pm$  2.4) PRP laser treatments since inclusion. At 24 months of follow-up, 21 BRVO patients (13.0%) had received macular laser treatment at least once, with an average of 1.4 ( $\pm$  0.7) macular laser treatments. Moreover, 29.6% of the BRVO patients (48 patients) had received at least once PRP laser treatment, with an average of 1.8 ( $\pm$  1.1) treatments by PRP laser since inclusion injection.

### **Safety**

Approximately half BRVO and CRVO patients had at least one AE during the 24-month study. The most common category of AE was ocular disorders (Supplementary Table 5). Five BRVO patients had 8 severe AEs possibly related to ranibizumab: macular ischemia, retinal ischemia, transient blindness and increased intraocular pressure (IOP), myocardial ischemia, lymphoma aggravation, cerebral infarction and hypertension. Two CRVO patients had 2 severe AEs possibly related to ranibizumab: transient ischemic attack and retinal ischemia. There were no fatal AEs related to ranibizumab. One BRVO patient experienced endophthalmitis, not related to ranibizumab at Month 18. No new safety findings were identified, and results were in line with the well characterized safety profile of ranibizumab.

### **Discussion**

This 24-month prospective multicenter observational study assessed real-world use and effectiveness of ranibizumab in patients with ME secondary to BRVO (and HRVO) and CRVO. Improvements in BCVA and CRT were observed at Month 3 and persisted up to Month 24 in both cohorts.

The BOREAL-RVO study was designed to include a real-life cohort of patients, representative of the wider RVO patient population. As such, the current study population had lower baseline VA for CRVO patients (40.4 [25.6] letters) compared to patients in the pivotal RCT CRUISE (48.1 [14.6] letters) [7]. For BRVO patients, baseline BCVA was similar in the current study (55.2 [18.7] letters) and in BRAVO (53 [12.5] letters) [8]. One possible explanation is that the current study included patient with ischemia, whereas they were excluded from the RCTs.

The inclusion of ischemic CRVO patients can explain why BCVA gains at Month 3 in CRVO patients were higher in the current study versus Month 3 BCVA gains in CRUISE [7]. These patients have a higher potential of BCVA gains, before encountering the “ceiling effect” seen elsewhere [9]. Indeed, mean (SD) baseline BCVA was higher in CRUISE (48.1 [14.6]) than for CRVO patients in the current study (40.4 [25.6] letters). The RAVE study also included ischemic CRVO patients, showing that lower baseline BCVA in such patients yielded notable BCVA gains (21.1 letters at Months 9) [10].

In the current study, ranibizumab treatment started with an induction period of three-monthly injections. Induction was completed for 79.9% of BRVO patients and 76.4% of CRVO patients. BCVA gains at Month 6 were numerically higher - although not statistically significant - for CRVO patients who completed the induction phase. However, patients who received more than 3 injections in the first 6 months had more gains > 5 EDTRS letters at 24 months ( $p=0.0064$ ). These results are in line with the large prospective LUMINOUS study, showing that an adequate loading dose led to numerically higher BCVA outcomes in both BRVO and CRVO patients at year 1 – although these were not statistically significant [11,12].

Up to Month 3, a similar pattern in improvements and gains in BCVA was noted in the current study versus the RCTs BRAVO and CRUISE [8, 7]. In the RCTs, BCVA gains continued to rise after Month 3, as patients were still being treated (6 monthly injections within the first 6 months), to reach a maximal BCVA at Month 6. This was not the case in the real-world BOREAL-RVO study.

After M3, the BCVA gains in the current study were lower than the gains observed in RCTs for BRVO and CRVO [8, 7], in line with the lower number of ranibizumab injections. In BRVO, the mean (SD) BCVA gain at Month 6 was 14.1 letters in the current study (for an average of 3.8 injections) compared to the BCVA gains at Month 6 in the BRAVO (18.3 letters for 6 injections) [8] and BRIGHTER (14.8 letters) RCTs [13]. Guidelines recommend that subsequent monthly injections must be continued until BCVA stability is reached [14], but they were not published at the time of the BOREAL-RVO study. Similarly, the BCVA gain at Month 24 of 11.4 letters in the current study was lower than the 17.5 letter gain reported in HORIZON, the 12-month extension of BRAVO. Indeed, BRVO patients had fewer injections over 24 months in the current study (7.2 injections) than in HORIZON, where patients in the 0.5 mg ranibizumab group had an average of 10.5 injections over 24 months [15].

In CRVO, the mean BCVA gains at Months 6, 12 and 24 were 9.5, 9.2 and 8.3 letters, respectively in the current study. These gains were lower than those reported in the RCTs CRUISE at Month 6 (14.9 letters) [7], CRYSTAL at Month 12 (12.3 letters) and Month 24 (12.1 letters) [9], and in HORIZON at Month 24 (12.0 letters) [15]. Again, the weaker gains in the current study were probably due to the lower number of injections over 24 months (7.1 injections) than in HORIZON (12.3 injections) or CRYSTAL (13.1 injections).

These real-life results on the use of ranibizumab in France mirror the outcomes observed in Germany. The OCEAN study included 744 patients with RVO between 2011 and 2015 and followed them up for 2 years. BCVA improved rapidly within the first 3 months, up to 10,7 letters gain at 12 months and 11,8 letters gain at 24 months after a median of 4 (5) injections over 12 (24) months [16]. At the same time in Portugal, a retrospective, observational, study including 200 patients treated with either ranibizumab or bevacizumab showed that median BCVA improved in both treatment groups in CRVO and BRVO patients at 6 months (-0,27 log MAR and -0,10 log MAR respectively) and 12 months (-0,26 log MAR and -0,10 log MAR respectively) compared to baseline ( $p < 0.001$ ). The median number of injections was 3 during the first 6 months and 1 from 6 to 12 months [17]. The 5 years worldwide LUMINOUS BRVO Study showed at Year 1 a mean VA gain equal to 11.9 letters from baseline with a mean of 5 ranibizumab injections in the 189 treatment naïve BRVO patients. VA gains were higher in patients who received 6-9 injections (13.6 letters) than in those who received 2-5 injections (11.7 letters), or 1 injection (3.6 letters) [11]. In the LUMINOUS CRVO Study at one year, 144 treatment naïve patients had a mean VA gain from baseline of 10.8 letters, with a mean of 5.4 ranibizumab injections [12]. LUMINOUS also underscored that outcomes vary across countries and are greatly affected by factors, such as treatment costs, reimbursement policies, ease of access to medicines, and sub-optimal treatment due to less strict follow-up measures in certain countries [11,12].

In the current study, BRVO patients had an average of 19.7 visits and 7.2 injections by Month 24, while CRVO patients had an average of 21.1 visits and 7.1 injections. This suggests that patients were adequately monitored but under-treated. Under-treatment has been observed in other real-world studies of ranibizumab in RVO, in other countries, at the same period [11,12,16-21]. It is highly likely that patients were treated under a pro-re-nata (PRN) regimen. In Switzerland, a retrospective case series of 76 RVO patients with consecutive recruitment within two different periods (PRN 2009–2012, treat and extend (T&E) 2012–2016) showed that T&E provided a better morphological outcome using more injections than PRN (9.6 and 4.2 at M12, respectively ( $p < 0.001$ )) [22]. At the time of the current study (between December 2013 and April 2015), the T&E regimen was not routinely used in RVO in France and became widespread only later on [23-25]. But as soon as 2010, in the US, a retrospective, interventional study including 60 CRVO eyes receiving T&E ranibizumab or bevacizumab showed that high VA gains were achieved at M12 (+12.8 ETDRS letters) with 8,1 injections (and visits) [26]. In 2016, in the UK, a retrospective analysis of 44 patients newly diagnosed with CRVO receiving T&E aflibercept showed that high VA gains were achieved at M12(+15.1 letters) with a mean number of injections (and visits) of 8 [27].

Of the patients still followed at Month 24, 85.8% of BRVO patients and 85.6% of CRVO patients experienced an interruption of ranibizumab treatment, mainly due to achievement of maximum BCVA and ME resolution or

regression. Considering the low proportion of “happy few” patients who completed induction without subsequent switch or additional injections due to favorable functional or anatomical outcomes (13.6% of BRVO patients and 12.2% of CRVO patients), treatment interruptions were indeed transient, and most patients usually warrant on-going monitoring as they will need to be treated again.

By Month 24, a third of patients had switched to other intravitreal treatments, mainly to aflibercept or dexamethasone implant. A few patients switched back to ranibizumab. The reasons for treatment switch were not collected. A small number of retrospective studies and small case series have investigated switching [28], as well as a small prospective trial which found that some patients unresponsive to one anti-VEGF treatment can benefit from switching to another [29].

In the current study, the proportion of patients with retinal ischemia, rubeosis iridis and other ophthalmologic comorbidities rose slightly from baseline throughout the study. Patients should continue to be monitored with fluorescein angiography to look for peripheral retinal non perfusion particularly when the treatment is stopped.

Lower baseline BCVA was predictive of higher BCVA gains at Month 6 for both BRVO and CRVO, which has already been demonstrated in previous studies [9,10]. Early BCVA gains by Month 3 were predictive of better gains at Month 6 and younger age at baseline was also predictive of better outcomes. In general, younger patients with less severe disease and in general good health had better improvements in BCVA. This supports findings from previous studies [4, 30-33]. As early as 1996, in 120 CRVO patients prospectively analyzed; older age, male gender, and the number of associated risk factors (systemic vascular risk factors and glaucoma) were found to be correlated with a poor visual outcome and with the development of retinal ischemia, as well as baseline visual acuity, initial extent of retinal non perfusion, and rheologic parameters (hematocrit, fibrinogen, and erythrocyte aggregation) [4]. As in our study, in the post hoc analysis of the prospective SHORE study, the only factors independently correlated with BCVA gain were younger age ( $p < 0.0001$ ) and worse baseline BCVA ( $P < 0.0001$ ) [32]. Several negative predictive factors for visual outcome based on OCT imaging were not assessed in the BOREAL-RVO study, but were found in later studies, such as the disruption of the external limiting membrane and ellipsoid zone [33].

There were no new safety findings in this study. Surprisingly, many ocular AEs previously reported with ranibizumab in RCTs and in other indications were not reported in this study. Therefore, these safety results should be interpreted with caution since AEs may be under-reported.

A strength of the current BOREAL-RVO study is that patients were included from a range of ophthalmologists throughout France, including private and hospital ophthalmologists. While this yielded a cohort which we believe to be representative of the wider population, several limitations could be associated with this approach. In accordance with the real-life observational study design, a range of scales were used to measure BCVA (Monoyer, Snellen and ETDRS). This could have led to loss of sensitivity. Among other limitations is the fact that a different pool of patients attended each visit (see Fig. 1) and the low patient sample with complete data, meaning these results should be interpreted with caution. Finally, the BOREAL-RVO study was performed in France, and it is not known whether these results can be extrapolated to other countries, especially because many other countries do not enjoy fully reimbursed healthcare.

## **Conclusion**

This BOREAL-RVO study showed that ranibizumab treatment in the real-life setting led to a rapid and considerable improvement BCVA and CRT at Month 3, mirroring clinical trials. After Month 3, because of under-treatment and despite regular follow-up, the outcomes were not maximized. This result was in favor of a change in RVO management practices in France towards a more proactive regimen (T&E). No new safety findings were identified in this 24-month study. In conclusion, the BOREAL-RVO study demonstrated ranibizumab to be a safe and effective treatment for BRVO and CRVO in the real-world setting.

## **Statements**

## **Acknowledgement**

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## **Statement of Ethics**

The study was conducted in France between December 2013 and April 2015 in accordance with the Declaration of Helsinki and complied with the relevant guidelines for human studies. Ethical approval was not required, according to French regulations for observational studies. The study was approved by the French agencies for data protection (CNIL) and health research data management (CCTIRS). Participating patients were informed about the study and signed informed consent forms.

## **Conflict of Interest Statement**

Dr. Agnès Glacet-Bernard has received consultancy fees from Novartis and Bayer.

Dr. Jean-François Girmens has received consultancy fees from AbbVie (Allergan), Bayer, Novartis and has stock ownership at Tilak Healthcare.

Pr. Laurent Kodjikian has received consultancy fees from AbbVie, Alimera, Bayer, Horus, Novartis, Roche.

Dr. Cécile Delcourt has received consultancy fees from Allergan, Chauvin-Bausch+Lomb, Novartis and Théa Pharma, and has received speaker fees from Apellis.

Dr. Franck Fajnkuchen has received consultancy fees from Allergan, Bayer, Horus and Novartis.

Pr. Catherine Creuzot-Garcher has received consultancy fees from AbbVie, Bausch+Lomb, Bayer, Horus, Novartis, Roche.

Pr. Pascale Massin has received consultancy fees from Novartis.

Nathalie San Nicolas is an employee of Novartis Pharma.

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This study was funded and sponsored by Novartis. The sponsor was involved in the collection and analysis of study data, and in preparation, revision and approval of the present manuscript.

## **Author Contributions**

Dr. Agnès Glacet-Bernard, Dr. Jean-François Girmens, Dr. Laurent Kodjikian, Dr. Cécile Delcourt, Dr. Franck Fajnkuchen, Pr. Catherine Creuzot-Garcher and Pr. Pascale Massin were involved in the planning, conduct, analysis, reporting of the study and revision of the manuscript. Dr. Agnès Glacet-Bernard and Nathalie San Nicolas wrote the manuscript with input of all other authors.

## **Data Availability Statement**

The datasets from the BOREAL-RVO study are not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author.

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## **Figures**

### **Figure 1. Flow chart of patients in study.**

BRVO=branch retinal vein occlusion, CRVO=central retinal vein occlusion

### **Figure 2. Treatment switch during study period.**

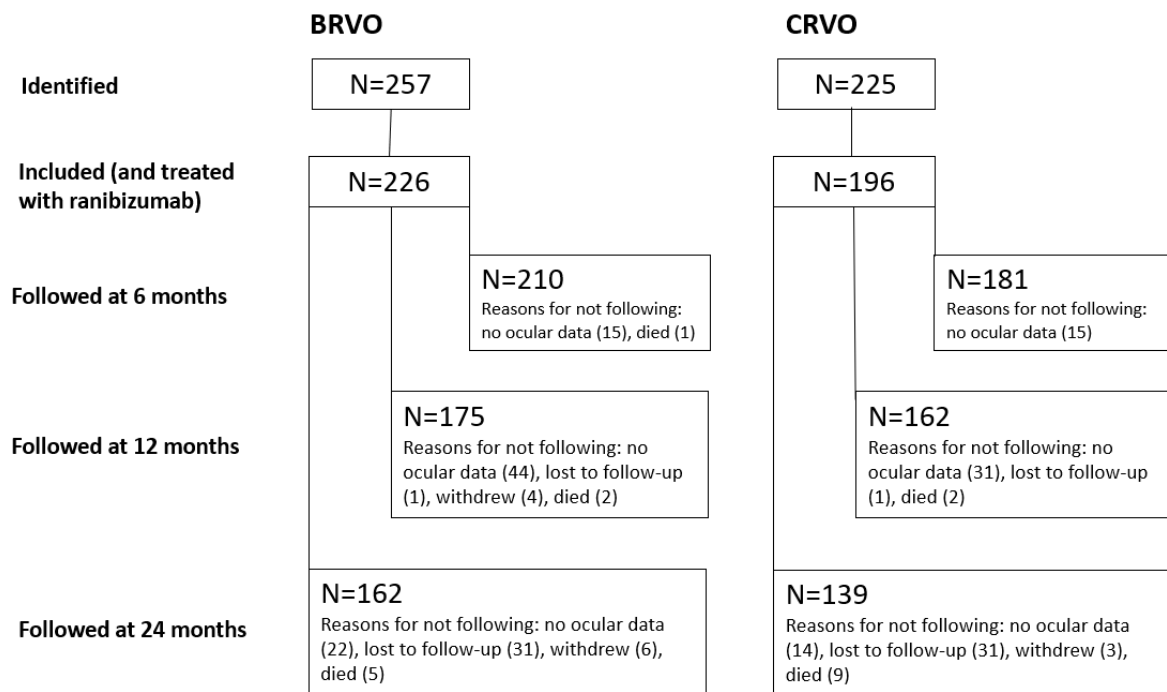
This chart describes how patients who initiated anti-VEGF therapy with ranibizumab (in the innermost ring) switched to other anti-VEGF treatments (shown in the outer rings, reading from the inside towards the outside). Each color represents a different anti-VEGF treatment. For example, 30.2% of BRVO patients switched treatment from ranibizumab: 15.4% to dexamethasone implant and 13.6% to aflibercept etc.

### **Figure 3. Change in Best-Corrected Visual Acuity.**

BCVA=best corrected visual acuity, BRVO=branch retinal vein occlusion, CRVO=central retinal vein occlusion, ETDRS=Early Treatment of Diabetic Retinopathy Study, n=number of patients with available data at each timepoint.

### **Figure 4. Change in Central Retinal Thickness.**

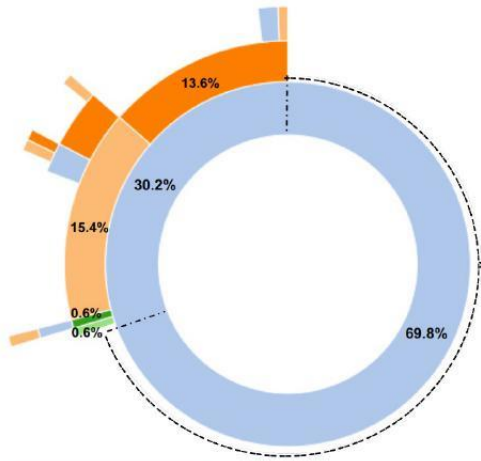
BRVO=branch retinal vein occlusion, CRT=central retinal thickness, CRVO=central retinal vein occlusion, n=number of patients with available data at each timepoint.



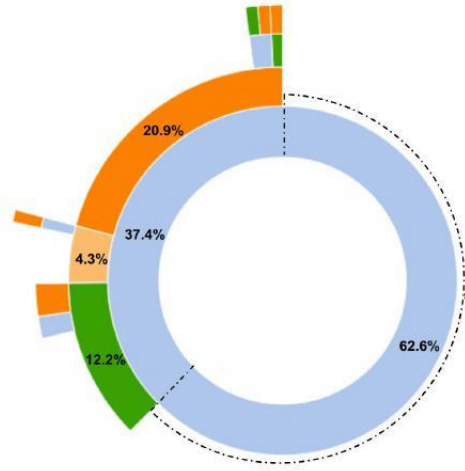
Accepted Manuscript

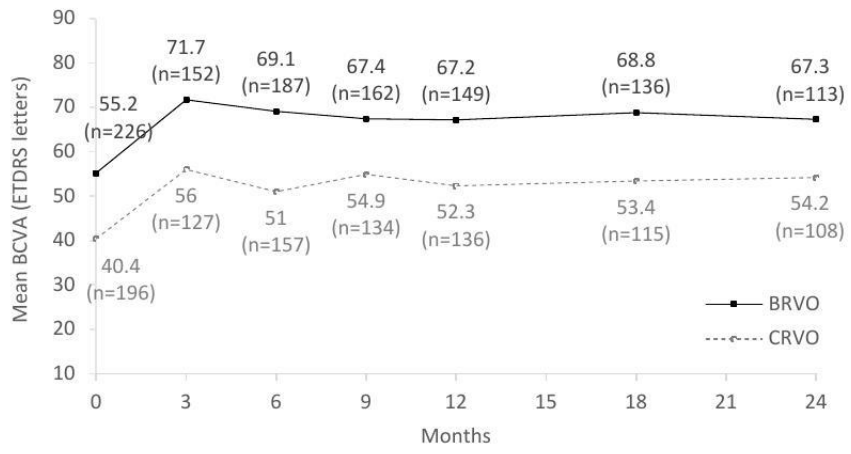


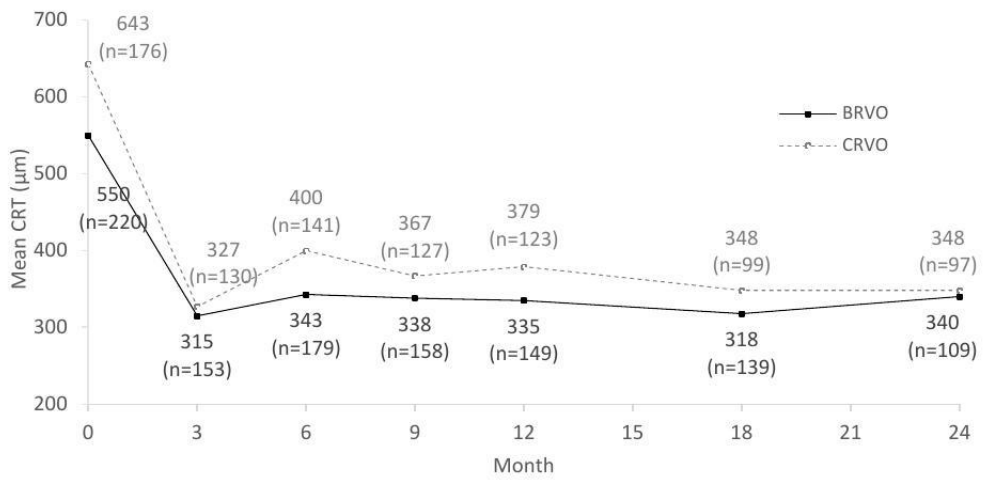
### BRVO



### CRVO







**Table 1. Baseline Characteristics**

<b>Number (%) of patients</b> Unless indicated otherwise	<b>BRVO</b> <b>N=226</b>	<b>CRVO</b> <b>N=196</b>
Male	110 (48.7)	101 (51.5)
Age (years), mean (SD)	70.9 (11.1)	70.4 (14.3)
Bilateral RVO	8 (3.5)	5 (2.6)
Time since first RVO symptoms in the studied eye (months), median [min;max]	1.0 [0.0;101.0]	0.8 [0.0;57.6]
Treatment-naïve in the studied eye patients	205 (90.7)	181 (92.3)
Previous ocular treatments in the studied eye for vision loss due to RVO (% of the eyes previously treated)	22 (9.7)	17 (8.7)
Laser	11 (50)	0 (0.0)
Bevacizumab	2 (9.1)	2 (11.8)
Dexamethasone implant	13 (59.1)	15 (88.2)
Aflibercept	0	0
Triamcinolone	1 (4.5)	1 (5.9)
Ranibizumab	0 (0.0)	0 (0.0)
BCVA (in ETDRS letters) in the studied eye		
Mean (SD)	55.2 (18.7)	40.4 (25.6)
Median [min;max]	59.0 [1.0;83.0]	44.0 (0.0;80.0)
BCVA category (in ETDRS letters) in the studied eye		
< 20 letters	11 (4.9)	42 (21.4)
20-58 letters	80 (35.4)	82 (41.8)
59-69 letters	69 (30.5)	41 (20.9)
≥ 70 letters	66 (29.2)	31 (15.8)
CRT (µm) in the studied eye, mean (SD)	549.9 (175.2)	643.5 (217.3)
Ocular comorbidities		
At least 1 ocular comorbidity	127 (56.2)	127 (64.8)
Cataract (un-operated)	61 (27.0)	58 (29.6)
Glaucoma or ocular hypertension	48 (21.2)	49 (25.0)
Complications		
Rubeosis iridis	1 (0.4)	8 (4.1)
Ischemia	74 (32.7)	75 (38.3)
Concomitant non-ocular disease		
Arterial hypertension	101 (57.4)	113 (57.7)
Diabetes	23 (13.1)	31 (15.8)
History of cardiovascular disease (myocardial infarction, arrhythmia etc.)	29 (16.5)	38 (19.4)
Migraine	6 (3.4)	10 (5.1)
History of stroke	114 (64.8)	5 (2.6)
Hypercholesterolemia	41 (23.3)	56 (28.6)
Concomitant anti-hypertension treatment		
None	102 (45.1)	84 (42.9)
1	60 (26.5)	40 (20.4)
2	38 (16.8)	45 (23.0)
3 or more	16 (7.1)	20 (10.2)

Percentages were calculated for patients with available data for each variable.

BCVA=best corrected visual acuity, BRVO=branch retinal vein occlusion, CRT=central retinal thickness, CRVO=central retinal vein occlusion, ETDRS=Early Treatment of Diabetic Retinopathy Study, RVO=retinal vein occlusion, SD=standard deviation

**Table 2. Frequency of ophthalmologist visits and anti-VEGF injections**

		<b>BRVO</b> <b>N=226*</b>	<b>CRVO</b> <b>N=196*</b>
<b>By Month 3</b>	N	224	195
	Visits, mean (SD)	4.0 (1.2)	4.2 (1.3)
	Injections, mean (SD)	2.8 (0.6)	2.7 (0.7)
<b>By Month 6</b>	N	210	181
	Visits, mean (SD)	6.9 (2.2)	7.3 (2.3)
	Injections, mean (SD)	3.8 (1.2)	3.6 (1.2)
<b>By Month 12</b>	N	175	162
	Visits, mean (SD)	12.3 (4.0)	12.6 (4.6)
	Injections, mean (SD)	5.5 (2.3)	5.1 (2.4)
<b>By Month 24</b>	N	162	139
	Visits, mean (SD)	19.7 (7.8)	21.1 (8.4)
	Injections, mean (SD)	7.2 (4.3)	7.1 (4.4)

\*Data are presented for the population of patients with available data at each timepoint

BRVO=branch retinal vein occlusion, CRVO=central retinal vein occlusion, SD=standard deviation, VEGF=vascular endothelial growth factor

**Table 3. Other Ocular Findings during Follow-up**

	BRVO			CRVO		
	Baseline n = 226	Month 6 n = 210	M24 n = 162	Baseline n = 196	Month 6 n = 181	M24 n = 139
Bilateral RVO, n (%)	8 (3.5)	8 (3.8)	9 (5.6)	5 (2.6)	7 (3.9)	6 (4.3)
Rubeosis iridis, n (%)	1 (0.4)	1 (0.5)	1 (0.6)	8 (4.1)	13 (7.2)	13 (9.4)
Ischemia, n (%)	74 (32.7)	84 (40.0)	79 (48.8)	75 (38.3)	84 (46.4)	74 (53.2)
Peripheral only	59 (26.1)	62 (29.5)	59 (36.4)	52 (26.5)	55 (30.4)	48 (34.5)
Macular and peripheral	9 (4.0)	13 (6.2)	13 (8.0)	20 (10.2)	25 (13.8)	23 (16.5)
Macular only	6 (2.7)	9 (4.3)	7 (4.3)	3 (1.5)	4 (2.2)	3 (2.2)
At least 1 ophthalmology comorbidity, n (%)	127 (56.2)	127 (60.5)	123 (75.9)	127 (64.8)	128 (70.7)	109 (78.4)
Cataract (un-operated)	61 (27.0)	54 (25.7)	48 (29.6)	58 (29.6)	57 (31.5)	43 (30.9)
Glaucoma and ocular hypertension	48 (21.2)	46 (21.9)	49 (30.2)	49 (25.0)	54 (29.8)	44 (31.7)
Pseudophakia	48 (21.2)	48 (22.9)	50 (30.9)	40 (20.4)	36 (19.9)	42 (30.2)
Intraocular pressure (mmHg), mean (SD)	15.3 (3.7)	15.4 (3.7)	15.8 (5.8)	15.8 (4.4)	16.2 (4.3)	15.8 (3.5)

BRVO=branch retinal vein occlusion, CRVO=central retinal vein occlusion, RVO=retinal vein occlusion, SD=standard deviation