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# Ranibizumab for Branch Retinal Vein Occlusion Associated Macular Edema Study (RABAMES): six-month results of a prospective randomized clinical trial

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**ABSTRACT.**

***Purpose:*** **To compare standard-of-care grid laser photocoagulation versus intravitreal ranibizumab (IVR) versus a combination of both in the treatment of chronic (>3 months) macular oedema secondary to branch retinal vein occlusion.**

***Methods:*** **Prospective, randomized, multicentre clinical trial. Thirty patients with a best-corrected visual acuity (BCVA) between 20/320 and 20/40 were randomized 1:1:1 to receive grid laser or three monthly injections of 0.5 mg IVR or both followed by 3 months of observation.**

***Results:*** **Mean change from baseline BCVA at month 6 was +2 letters [laser; 0.04 logMAR, 95% confidence interval (−0.17; 0.25)], +17 letters [IVR; 0.34 (0.19; 0.5)] and +6 letters [combination; 0.12 (0.01; 0.24)] (IVR versus laser p = 0.02 and IVR versus combination p = 0.02). At month 3, mean improvement in central retinal thickness (CRT) was 90.6 µm (laser) (−18.65; 199.8), 379.5 µm (IVR) (204.2; −554.8), and 248 µm (167.2; −328.8) (combination) (IVR versus laser p = 0.005, laser versus combination p = 0.02). During the observation period, CRT improved in laser [37.6 µm (−66.82; 142.0)], but deteriorated in IVR [−142.4 µm (−247.6; −37.16)] and combination [−171.7 µm (−250.4; −92.96)] (laser versus IVR p = 0.01, laser versus combination p = 0.002) indicating recurrent oedema. Less laser retreatments (at 8 weeks) were required in combination group (2/10) than grid group (7/10).**

***Conclusion:*** **Six-month results suggest that ranibizumab may be superior to grid laser in improving visual acuity. Grid combined with IVR neither enhanced functional and morphological improvement of IVR nor did it prevent or prolong recurrence of oedema. In IVR groups, CRT increased slowly after stopping injections, whereas improvement in visual acuity was sustained, indicating that morphological changes occur prior to functional impairment.**

**Key words:** anti-VEGF – branch retinal vein occlusion – grid laser – intravitreal injections – macular oedema – ranibizumab

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## Introduction

For several decades, grid-pattern laser photocoagulation has been the gold standard in the treatment of chronic macular oedema secondary to branch retinal vein occlusion (BRVO) (The Branch Vein Occlusion Study Group 1984; Esrick et al. 2005; Mirshahi et al. 2008; Riese et al. 2008). The Collaborative Branch Vein Occlusion Study (BVOS) reported 65% of treated eyes gained two or more lines in best-corrected visual acuity (BCVA), compared to 37% of untreated eyes (The Branch Vein Occlusion Study Group 1984). The average gain in BCVA after 3 years was one Snellen line.

Retinal vein occlusions are associated with increased intravitreal levels of vascular endothelial growth factor (VEGF) as well as inflammatory factors (Aiello et al. 1994; Noma et al. 2006; Ehlken et al. 2011). Intravitreal agents such as triamcinolone (Scott et al. 2009), dexamethasone (Haller et al. 2010) and VEGF-Inhibitors, upon them ranibizumab (Campochiaro et al. 2010; Brown et al. 2011) and bevacizumab (Russo et al. 2009) demonstrated efficacy in the therapy of macular oedema secondary to BRVO (Pielen et al. 2013). In the BRAVO trial, monthly intravitreal ranibizumab (0.5 mg) led to a significant visual improvement (≥15 letters) in 61.1% of

treated eyes as compared to 28.8% in the sham group after 6 months (Campochiaro et al. 2010). The mean visual improvement was 18.3 letters in ranibizumab-treated patients and 7.3 letters in the sham group. Major limitation of BRAVO was the lack of comparison between ranibizumab and standard-of-care grid laser photocoagulation. Rescue grid laser photocoagulation was permitted in all groups, so that the effects of deferred grid treatment cannot be assessed nor compared. Less patients received grid laser treatment within the ranibizumab groups compared to the sham group (19.8% IVR 0.5 mg, 18.7% IVR 0.3 mg, 54.5% sham) (Campochiaro et al. 2010). SCORE study did not find a significant effect of intravitreal triamcinolone compared to standard-of-care grid laser photocoagulation and suggested to test any intravitreal treatment for macular oedema in BRVO against standard-of-care grid (Scott et al. 2009). Anti-VEGF therapy, however, has widely replaced laser treatment as the standard-of-care. To date, only one randomized prospective trial directly compared the relative efficacy of ranibizumab monotherapy and grid laser photocoagulation in BRVO (Tan et al. 2014). Six monthly injections of ranibizumab 0.5 mg followed by PRN treatment led to a mean change of BCVA of +12.5 letters at month 12 compared to a mean loss of 1.6 letters in the standard-of-care group (six sham injections followed by PRN sham injections). Grid laser could be applied at weeks 13 and 25 in both groups according to BVOS criteria and was applied more frequently in the standard-of-care group (68.4, 50.0%) than in ranibizumab-treated patients (6.7%, 8.3%) (Tan et al. 2014). Functional results of ranibizumab stay behind BRAVO results and grid results behind SCORE results which may be attributable to a small sample size and high dropout rate in the standard-of-care group (completion rate: 14/15 ranibizumab, 16/21 standard-of-care).

The aim of this prospective randomized trial, which was initiated and recruited before and in parallel to the BRAVO study and the comparative trial by Tan et al., was to compare visual and morphological outcomes after treatment with standard-of-care grid laser photocoagulation, intravitreal ranibizumab, or a combination of both in eyes with chronic macular oedema secondary to BRVO. Strengths of our study design are the direct comparison of grid versus ranibizumab and ranibizumab versus combination to overcome limitations of BRAVO and Tan's study (all groups received rescue grid, unclear additive effect in combination group). We divided our study into a treatment phase followed by an observational phase to investigate the course of morphological and functional effects after initial treatment. Results will add knowledge to the ongoing discussion of response-to-treatment and choice of treatment regimen in macular oedema due to BRVO.

# Methods

The Ranibizumab for Branch Retinal Vein Occlusion Associated Macular Edema Study (RABAMES) is a prospective, randomized, controlled, multicentre investigator-initiated clinical trial evaluating the efficacy of intravitreal ranibizumab versus grid-pattern laser photocoagulation versus a combination of both in patients with chronic macular oedema secondary to BRVO. At baseline, criteria for standard-of-care grid laser treatment due to chronic perfused macular oedema as defined according to the BVOS had to be fulfilled (duration of symptoms and/or diagnosis for longer than 3 months and less than 18 months) (The Branch Vein Occlusion Study Group 1984). After a screening period of up to 2 weeks (days −14 to −1), patients were treated for 3 months (day 0 to week 12) according to their assigned group followed by a 3-month observation period (weeks 12–24). During the 3-month treatment period, patients received either three monthly intravitreal ranibizumab injections (0.5 mg in 0.05 ml, Lucentis®; Novartis Pharma, Nuremberg, Germany) or up to two treatment sessions of macular laser photocoagulation (day 0 and at day 54–58, if needed) or intravitreal ranibizumab combined with laser photocoagulation (Table 1).

The RABAMES trial was performed in accordance with the tenets of the declaration of Helsinki and was prospectively assessed and approved by all responsible institutional review boards, by the Paul-Ehrlich-Institute, the Federal Institute for Vaccines and Biomedicines in Germany and by the local authorities of all study sites (protocol number AU-06104G/Rabames-Studie, EudraCT number 2006-006131-53). The trial is registered at www.clinicaltrials.gov (NCT00562406). All patients were instructed and gave written informed consent prior to any study-related activities.

### Screening and eligibility

Consecutive BRVO patients visiting a site during the study were screened for eligibility according to protocol criteria (Table 2). Only one eye per patient was included in the study. After the informed consent process, a general and ophthalmic medical history was obtained from each subject, and all patients underwent a complete eye examination including BCVA according to the Early Treatment of Diabetic Retinopathy (ETDRS) protocol, slit lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, fluorescein angiography (FA), and optical coherence tomography (OCT). The Stratus 3® or Cirrus® OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) was used to determine the central retinal thickness (CRT). All patients were followed using the same OCT device throughout the study. OCT scans were evaluated by an independent retina specialist masked to the individual treatment. On FA, macular oedema had to fulfil the criteria for laser treatment according to the Collaborative Branch Vein Occlusion Study (The Branch Vein Occlusion Study Group 1984). Patients with evidence of macular ischaemia, central subretinal fibrosis or atrophy, persistent haemorrhages or retinal neovascularization were excluded. The investigating physician and principal investigator at each study site determined eligibility.

### Randomization

Patients were randomized 1:1:1 to one of three study arms (ranibizumab versus laser versus combination). Randomization was performed by the coordinating study centre (Ludwigshafen). The randomization list implemented blocked randomization with one block of size 30 (10 eyes and patients per study arm) without any stratification. This procedure guaranteed overall balance of study arms and

treatment concealment. Screening log, randomization number and assigned treatment group were kept by the principal investigator at each site.

### Grid laser photocoagulation

Patients in the laser and combination subgroups received grid laser photocoagulation at day 0 and an optional second laser at visit 6 (day 54–58), both guided by FA. Areas of intraretinal haemorrhages were avoided at baseline treatment. If resorption of haemorrhages occurred, laser treatment could be completed at visit 6. Laser photocoagulation was performed with a grid pattern as recommended by the Collaborative Branch Vein Occlusion Study (The Branch Vein Occlusion Study Group 1984). Argon green-blue laser was recommended lasting 0.1 second, at 100 micron diameter and a power setting sufficient to produce a medium white burn. No further laser treatment was planned during the observation period.

### Intravitreal injections

Patients in the ranibizumab or combination subgroups received three monthly intravitreal ranibizumab injections according to a unified protocol as described previously (Campochiaro et al. 2010). Intravitreal injections were performed under sterile conditions in an operation theatre as outpatient procedure. No further intravitreal injections were administered during the 3-month observation period.

### Combination group

At baseline, patients randomized to the combination group first received laser treatment as outlined above and first intravitreal ranibizumab on the same day with a minimum of 30 min between laser and intravitreal injection. Second intravitreal ranibizumab was given at visit 4 (day 26–30, Table 1). A second laser treatment could be applied at visit 6 (day 54–58), if considered necessary by the investigator. Criteria for the additional treatment were persistent macular oedema in FA with foveal impairment and resorption of initial haemorrhages in areas that had to be spared at baseline. Laser treatment was performed on the same day as the third intravitreal injection with a minimum of 30 min between laser and injection.

### Outcome measures

The primary outcome measure was mean change in BCVA (logMAR) from baseline at month 6 (presented in ETDRS letters for better comparison between trials). Secondary outcome measures included mean change in BCVA at month 3, percentage of patients who improved by or lost ≥15 letters of BCVA from baseline at month 3 and 6, mean change in CRT by OCT from baseline at months 3 and 6, and mean change in CRT by OCT from month 3 to 6. Ocular or systemic adverse events and serious adverse events throughout the study period were considered as safety outcome measures and evaluated at each visit. Ocular adverse events considered as possibly related to study treatment included endophthalmitis, progression of cataract or cataract surgery, retinal tear, retinal detachment, vitreous haemorrhage, conversion from non-ischaemic to ischaemic perfusion status, or development of retinal or anterior segment neovascularization.

### Imaging protocol

The Stratus 3® or Cirrus® OCT (Carl Zeiss Meditec Inc.) was used to determine CRT. Three centres used Stratus 3 and examined 26/30 patients (group distribution: laser $n = 9$, ranibizumab $n = 9$, combination $n = 8$), one centre obtained images with the Cirrus (laser $n = 1$, ranibizumab $n = 1$, combination $n = 2$). CRT was measured by OCT at baseline, visit 2 (day 5–7), visit 3 (day 24–28), 5 (day 52–56), 7 (week 12), 8 (week 18), and 9 (week 24). Fast macular thickness scan was obtained and analysed per macular thickness map. Scans were checked for correct automated CRT measurement. In case of software algorithm failure or poor image quality, CRT was remeasured manually in all six individual scans and mean CRT was calculated. The examiner reassessing the images was masked

**Table 1.** Visit schedule.

| | Visit | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Action | Screening | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 | Visit 9 |
| Trial day | −14 to −7 | 0 | 5 to 7 | 24 to 28 | 26 to 30 | 52 to 56 | 54 to 58 | Week 12 | Week 18 | Week 24 |
| Patient information and consent | X | | | | | | | | | |
| History and anamnesis | X | | X | X | | X | | X | X | X |
| Inclusion/exclusion criteria (general and ophthalmologic) | X | | | | | | | | | |
| Vital signs | X | X | | | X | | X | | | X |
| Pregnancy test in women of child-bearing potential* | X | | | X | | X | | X | | X |
| Basic Ophthalmologic examination | X | | X | X | | X | | X | X | X |
| Fluorescein angiography | X | | | X | | X | | X | X | X |
| Optical coherence tomography | X | | X | X | | X | | X | X | X |
| Randomization | | X | | | | | | | | |
| Laser photocoagulation | | X* | | | | | X* | | | |
| Intravitreal injection | | X* | | | X* | | X* | | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X |
| End of trial | | | | | | | | | | X |

* Depending on the assigned study arm.

**Table 2.** Main inclusion and exclusion criteria.

Key inclusion criteria
- Adults aged 18 years and older with chronic (> 3 months, < 18 months) macular oedema secondary to branch retinal vein occlusion
- Patients who at baseline have a BCVA in the study eye between 20/320 and equivalent to 20/40, using an ETDRS chart
- All of the following characteristics as determined by fluorescein angiography and OCT:
  - Evidence that the macular oedema extends under the geometric centre of the foveal avascular zone.
  - Evidence that the oedema is only secondary to BRVO (no other relevant ocular diseases, e. g. uveitis).
  - Evidence that central retinal thickness is > 225 μm.
  - Evidence that the oedema was suitable for BVOS laser criteria, that is, did not show macular ischaemia, central subretinal fibrosis or atrophy, or central persistent hermorrhage.
- Only one eye of a patient may be included.

Key exclusion criteria
- Patients who at baseline
  - have a relevant ocular disease potentially associated with increased intraocular VEGF levels (namely uveitis, neovascular glaucoma, neovascular age-related macular degeneration, diabetic retinopathy, diabetic maculopathy, ocular ischaemic syndrome and others)
  - have a relevant malignant systemic disease possibly associated with increased systemic VEGF levels (e.g. breast cancer)
  - had undergone treatment for macular oedema (e.g. laser, triamcinolone, vitrectomy, etc.)

BCVA = best-corrected visual acuity; VEGF = vascular endothelial growth factor.

to the treatment group. Colour fundus photography and fluorescein angiography were obtained due to the trial schedule at baseline and visits 3, 5, 7, 8, 9 (Table 1). Images were captured during the transit phase from 15 to 45 seconds, at 1 min and at 5 min.

### Statistical analysis

Changes in BCVA from baseline to month 6 were analysed in a linear regression model including study arm and baseline BCVA values as independent predictors. ANOVAs were then performed to compare the study arms by the mean change from baseline to months 3 and 6. The same statistical tests were used to compare the study arms by mean change in CRT from baseline to months 1, 3, 6 and between months 3 and 6.

The proportion of patients who gained ≥15 letters of BCVA from baseline to month 3 and month 6 was calculated, and Fisher′s exact test was performed to analyse the impact of the three study arms by their gain or loss of letters. Fisher′s exact test and ANOVA were computed to control that gender, age and preoperative BCVA were equally distributed between the three treatment groups.

At the planning stage of the study, we had no estimates available for the effects of intravitreal ranibizumab treatment for macular oedema in BRVO. This study had been planned as a pilot study (proof-of-concept) to acquire an estimate of the effects in direct comparison between grid, intravitreal ranibizumab and combination. All p-values are considered as explorative; no significance level has been fixed. Analysis was performed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA). Data were analysed according to the group to which they were originally assigned.

# Results

### Baseline characteristics and patient demographics

Between April 2008 and March 2010, 38 treatment naïve patients were screened and 31 eyes of 31 patients were randomized. One dropout occurred, resulting in 10 patients per treatment arm (see patient flow chart, Fig. 1). Patient demographics and baseline characteristics are summarized in Table 3. At baseline, there was no statistically significant difference between the three study groups. All patients received the randomized procedure. Seven of 10 patients in the laser group and two of 10 patients in the combination group received two laser treatments.

### Functional outcomes at month 6

Ranibizumab alone or in combination with grid lasercoagulation led to significant mean visual improvement [logMAR (95% CI)] from baseline BCVA at month 6: +17 letters [0.34 logMAR (0.19; 0.5)] in the ranibizumab group and +6 letters [0.12 logMAR (0.01; 0.24)] in the combination group, compared to stable vision in the laser group [+2 letters, 0.04 logMAR (−0.17; 0.26), p = 0.02 for IVR versus laser group and p = 0.02 for IVR versus combination group, Fig. 2]. Significant improvement in visual acuity of three or more lines at month 6 was gained by 7/10 of both ranibizumab groups, compared to 2/10 (laser) (p = 0.04). More ranibizumab-treated patients (7/10) presented a Snellen equivalent BCVA of ≥20/40 compared to the other groups (laser 5/10; combination 6/10, p = 0.89). No patient in the ranibizumab groups lost three or more VA lines, while one laser patient did.

### Morphological outcomes at month 6

At month 6, mean decrease of CRT [μm (95% CI)] was 128.2 μm (−86.7 μm; 232.9 μm) in the laser group, 237.1 μm (91.8 μm; 382.4 μm) in the ranibizumab group and 97.7 μm (10.8 μm; 184.6 μm) in the combination group (p = 0.10 for IVR versus laser group and p = 0.08 for IVR versus combination group, Fig. 3). After 6 months, a CRT ≤250 μm was observed in 1/10 laser-treated patients, in 5/10 ranibizumab-treated patients and in 0/10 patients who received a combined treatment (p = 0.03 for IVR versus laser or combination).

### Comparison of effects during treatment phase and observation period

*Functional outcomes*

Mean visual improvement [logMAR (95% CI)] from baseline BCVA at month 3 was more pronounced in ranibizumab groups with +17.5 letters [0.35 logMAR (0.23; 0.48)] IVR and +12 letters [0.24 logMAR (0.16; 0.33)] combination, than laser +4.5 letters [0.09 logMAR (−0.10; 0.28)] (p = 0.02 for IVR versus laser group and p = 0.12 for IVR versus combination group, Fig. 2). The percentage of patients who gained 3 or more lines was 8/10 (IVR), 2/10 (laser) and 3/10 in the combination group (p = 0.02 for IVR versus laser or combination). Nine of 10 ranibizumab-treated patients had

a BCVA of ≥20/40 (laser 5/10; combination 8/10; p = 0.15).

From month 3 to month 6, mean visual acuity remained fairly stable and decreased only slightly by 2.5 letters [0.05 logMAR (−0.19; 0.09)] in the laser group and 0.5 letter [0.01 logMAR (−0.08; 0.06)] in the ranibizumab group. We noted a sudden drop in the combination group from week 18 to 24, resulting in a difference of −5 letters [0.10 logMAR (−0.2; 0.01)] compared to month 3 (p = 0.57 for IVR versus laser group and p = 0.14 for IVR versus combination group, Fig. 2). This was due to loss of −5 to −17 letters in 7 patients in the combination group, while only two ranibizumab patients lost −5 to −8 letters from month 18 to 24 (Supplementary table).

*Morphological outcomes*

In analogy to results in BCVA, CRT [μm (95% CI)] at month 3 was most reduced in ranibizumab groups by 379.5 μm (204.2; 554.8) IVR and 248 μm (167.2; 328.8) combination, compared to a mean decrease of 90.6 μm (−18.6; 199.8) in the laser group (p = 0.005 for IVR versus laser group, p = 0.02 for laser versus combination group and p = 0.15 for IVR versus combination group, Fig. 3). No patient in the laser group presented with CRT <250 μm, while we found 8/10 patients in the ranibizumab group and 6/9 (CRT measurement missing in one patient) in the combination group.

During the observation period from month 3 to month 6, mean CRT [μm (95% CI)] decreased further in the laser group [37.6 μm (−66.82 μm; 142.0 μm)], whereas we observed an increase of CRT in the IVR group [−142.4 μm (−37.16 μm; −247.6 μm)] and in the combination group [−171.7 μm (−92.96 μm; −250.4 μm), p = 0.01 for IVR versus laser group, p = 0.002 for laser versus combination group, and p = 0.62 for IVR versus combination group] (Fig. 3).

*Safety outcomes*

Safety assessment included all patients who underwent at least one injection of ranibizumab or one laser treatment (*n* = 31). No sight-threatening ocular adverse events were observed. Non-ocular serious adverse events included one case of stroke after the first intravitreal injection of ranibizumab which resulted in study discontinuation according to the patient's decision. This patient was taken into account in the safety evaluation but not the efficacy assessment. All other patients completed the study per protocol through month 6. None of the patients developed macular ischaemia or retinal or anterior segment neovascularization or required treatment with scatter laser photocoagulation.

# Discussion

Results from the first prospective randomized clinical BRAVO trial led to a paradigm change in treatment of macular oedema due to BRVO and to approval of intravitreal ranibizumab (Campochiaro et al. 2010; Brown et al. 2011). However, BRAVO was limited by the lack of direct comparison of ranibizumab to standard-of-care grid laser treatment as demanded by the SCORE study group. Additionally, comparison

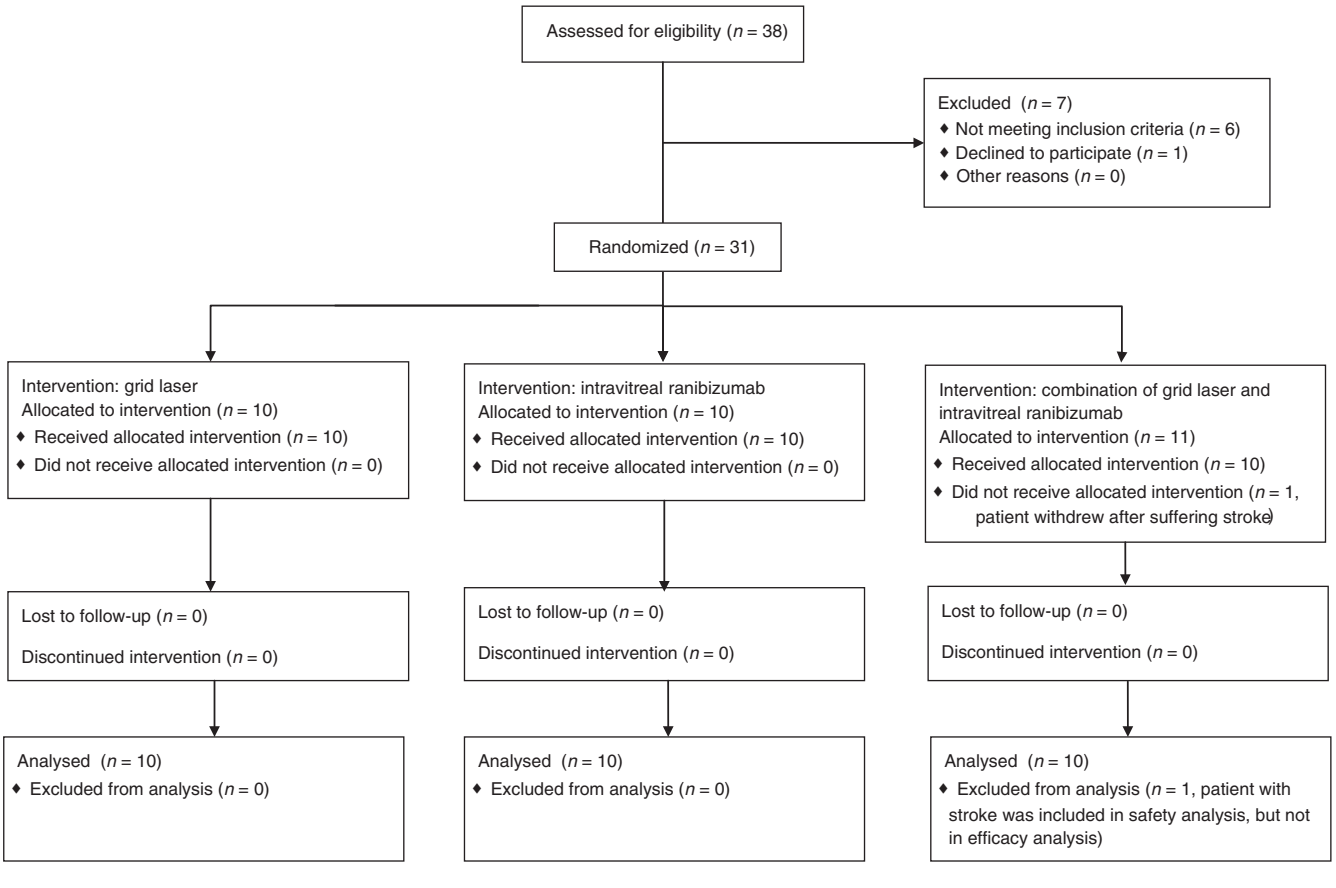


**Fig. 1.** RABAMES patient flow diagram according to the Consolidated Standards of Reporting Trials (CONSORT) illustrating the screening, randomization, treatment and analysis phases of the trial.

**Table 3.** Demographic data and baseline ocular characteristics.

| Parameter | Grid Laser ($n$ = 10) | Ranibizumab ($n$ = 10) | Laser+Ranibizumab ($n$ = 10) |
|---|---|---|---|
| Age (year) | | | |
| Mean (SD) | 68.8 (9.5) | 64.2 (8.6) | 65.9 (11.2) |
| Median | 70.5 | 67.5 | 67.5 |
| Range | 53–82 | 49–76 | 43–78 |
| Gender, $n$ (%) | | | |
| Male | 5 (50) | 4 (40) | 6 (60) |
| Female | 5 (50) | 6 (60) | 4 (40) |
| BCVA logMAR | | | |
| Mean (SD) | 0.52 (0.13) | 0.53 (0.24) | 0.41 (0.11) |
| Range | 0.3–0.8 | 0.3–1.1 | 0.3–0.68 |
| Approximate Snellen equivalent | 20/63 | 20/63 | 20/50 |
| CRT | | | |
| Mean (SD) | 570.6 (158.1) | 584.2 (250.9) | 505.6 (81.8) |
| Range | 329–850 | 228–1030 | 367–634 |
| Duration, months | | | |
| Mean (SD) | 5 (2.4) | 5.1 (3.5) | 6.0 (4.2) |
| Range | 3–10 | 3–13 | 3–12 |

BCVA = best-corrected visual acuity; CRT = central retinal thickness; SD = standard deviation; Duration = time between onset of symptoms and screening for participation in the RABAMES trial.

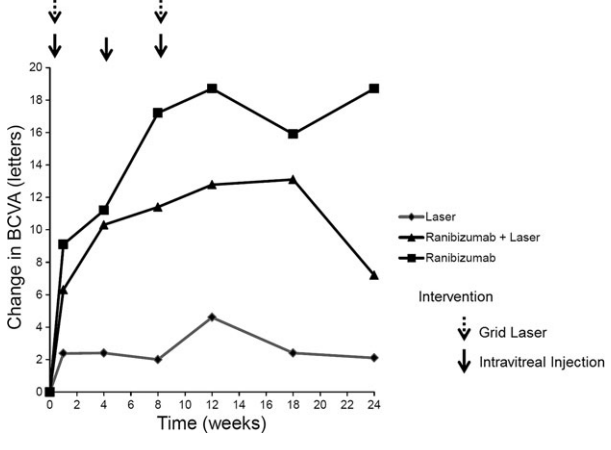


**Fig. 2.** Change of best-corrected visual acuity [BCVA (letters)] from baseline to month 6. Mean change from baseline was +2 letters [0.04 logMAR (−0.17; 0.25)] in the laser group, +17 letters [0.34 logMAR (0.19; 0.5)] in the ranibizumab and +6 letters [0.12 logMAR (0.01; 0.24)] in the combination group (IVR versus laser p = 0.02 and IVR versus combination p = 0.02). Note that the treatment period was 12 weeks followed by an observation period until week 24.

between patients with sham injection versus grid rescue versus ranibizumab versus ranibizumab plus grid rescue treatment was not possible. It remained unclear, if additive grid laser would alter the functional or morphological changes after ranibizumab treatment and impossible to assess an additional effect to ranibizumab monotherapy.

In our study, ranibizumab was directly compared to standard-of-care grid laser and a combination. At baseline, all RABAMES patients fulfilled BVOS criteria for grid laser treatment. No patient received any treatment before 12 weeks of BRVO duration. This design guaranteed best comparability between groups. As a consequence, time from diagnosis of BRVO to treatment differs between RABAMES (5.1 months, treatment at baseline) and BRAVO (3.3 months at baseline, grid rescue therapy at +3 months) and Tan et al. (16.3 weeks, grid at +13 weeks).

Today we know that observation is no longer an acceptable therapeutic approach to macular oedema in retinal vein occlusion (Pielen et al. 2013). Consistently, sham patients that received study drug after 6 months did not respond as well as treatment groups in all randomized controlled trials regardless of the intravitreal treatment (ranibizumab (BRAVO/CRUISE), bevacizumab (Epstein), dexamethasone implant (GENEVA)). We did not have this knowledge at the planning of our study. Neither could we foresee the reaction to different treatment regimen. Seen from today, our study design with a treatment phase followed by an observation period might be considered unusual and off standard-of-care because the recurrent oedema seems predictable (due to current knowledge), and ranibizumab/combination patients may have had a further visual improvement with further injections until month 6. BRAVO and Tan et al. used 6 monthly ranibizumab injections, but treatment regimen in "real-world" settings vary a lot and often favour a 3-injection upload followed by PRN. With our unique design, we may add valuable information on the course of functional and morphological effects until 6 months following each of the three treatments and address the following questions: Would grid be able to prevent or delay the recurrence of macular oedema in the combination group? Do morphological and functional changes occur simultaneously? Secondary analysis of BRAVO found a predictive value for early versus late ranibizumab response determined by OCT, "early" being exactly the 3-month time point we focused on (Bhisitkul et al. 2013).

In accordance with BRAVO and other randomized controlled trials investigating intravitreal therapy for BRVO, we chose a 6-month period for primary outcome, although laser effects may slowly continue over a long term as seen in BVOS (The Branch Vein Occlusion Study Group 1984). It was beyond the scope of RABAMES to evaluate clinical outcomes after treatment in the immediate early phase after BRVO. The presence of intraretinal haemorrhages and oedema in early BRVO often precludes grid laser photocoagulation for several months, while anti-VEGF therapy is not limited and results seem to be better the earlier it starts (Campochiaro et al. 2010; Pielen et al. 2013). These circumstances impede a direct comparison of laser with VEGF inhibitor therapy in patients with recent-onset BRVO.

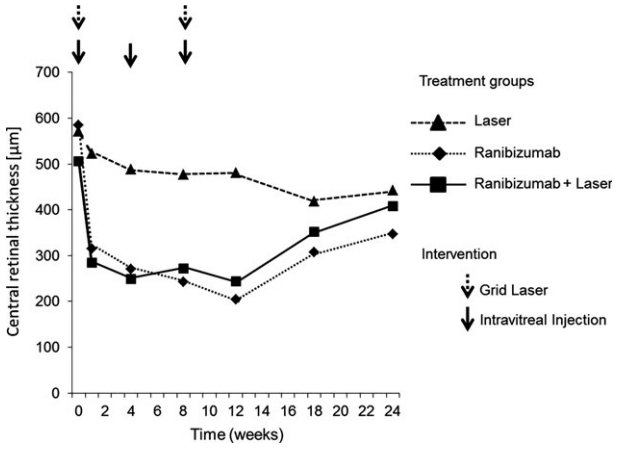


**Fig. 3.** Central retinal thickness [CRT (µm)] measured by optical coherence tomography from baseline to month 6. We observed a pronounced decrease in CRT during the treatment phase (until week 12) among those patients who received ranibizumab monotherapy (IVR) or a combination of ranibizumab and laser (IVR versus laser p = 0.005, laser versus combination p = 0.02, IVR versus combination p = 0.15). During the observation period from month 3 to month 6, mean CRT decreased in the laser group, whereas we observed an increase in the IVR group and in the combination group (IVR versus laser p = 0.01, laser versus combination p = 0.002, IVR versus combination p = 0.62).

**Results of IVR and comparison to BRAVO**

In RABAMES, we found that ranibizumab monotherapy was more effective than standard-of-care grid laser photocoagulation for chronic perfused macular oedema in BRVO. Grid combined with ranibizumab neither enhanced functional and morphological improvement of ranibizumab nor did it prevent or prolong recurrence of oedema. Improvement of BCVA and decrease of macular thickness are in line with BRAVO results (Campochiaro et al. 2010). Ranibizumab patients improved by 17 letters compared to 18.3 (BRAVO), gained ≥15 letters in 70% (RABAMES) and 61.1% (BRAVO), resulting BCVA ≥20/40 was 70% and 65%, respectively. CRT reduction in ranibizumab patients (380 µm/3 months and 237 µm/6 months) was similar to BRAVO (330 and 354 µm, respectively) (Campochiaro et al. 2010). Results are similar despite the different design and baseline characteristics (three injections plus observation versus 6 monthly injections, time from diagnosis to ranibizumab treatment 5.1 months versus 3.3 months).

**New insight from observation period (IVR)**

We observed a prompt and comparable improvement in BCVA after three intravitreal ranibizumab injections (+17.5 letters) that was contained over the observation period (+17 letters). In contrast, we observed a characteristic morphological improvement at months 3 (380 µm) and a slow pronounced deterioration after cessation of ranibizumab. This finding supports the hypothesis that morphological changes precede functional impairment (Kang et al. 2013) and might be helpful in defining re-injection criteria or clinical practice guidelines (Germany Ophthalmology Society, Retina Society & Professional Association of German Ophthalmologists 2012). RABAMES patients might have profited from ongoing ranibizumab compared to observation, but the difference in BCVA is small (+17.5 letters/3 months and +17 letters/6 months versus 18.3 letters BRAVO). Response to ranibizumab treatment (CRT ≤250 µm at month 3) was similar between Rabames (80%) and BRAVO (84.7%) predicting a comparable prognosis (Bhisitkul et al. 2013).

**Results of grid and comparison to BVOS (grid), BRAVO and Tan (sham plus rescue grid)**

Results of laser-treated patients are fairly comparable between RABAMES and BVOS given the difference in number of participants and duration of follow-up (The Branch Vein Occlusion Study Group 1984). Improved vision (defined as ≥2 lines or 10 letters according to BVOS) after 6 months was 40% compared to 65% in BVOS after 3 years, BCVA ≥20/40 was 50% (RABAMES) and 60% (BVOS). RABAMES strengths are inclusion and treatment criteria according to BVOS for all treatment arms. Our laser group was first treated at baseline with an optional additive laser treatment after 8 weeks. In contrast, BRAVO and Tan et al. included patients after shorter duration of BRVO into control groups, which received sham injections and observation until month 3/week 13, when grid laser treatment was performed as rescue therapy (Campochiaro et al. 2010; Tan et al. 2013). Grid was performed in 54.5% (BRAVO) and 68.4% (Tan). BCVA: In our study, visual improvement remained at baseline levels (+4.5 letters/3 months and +2 letters/6 months) after grid treatment, while CRT slowly continued to decrease (−90.6 µm/3 months, additional −37.6 µm/6 months). This is in line with SCORE (+4.2 letters) (Scott et al. 2009), similar to BRAVO sham/grid rescue patients who showed approximately +3.5 letters from 3 to 6 months and gradual decrease of CRT (Campochiaro et al. 2010). Tan et al. (2014) observed visual improvement from month 3 onwards when rescue treatment started that did not lead to any improvement compared to baseline.

**Results of combination group and comparison**

RABAMES combination of intravitreal ranibizumab and grid was not superior to ranibizumab alone. We observed an improvement in response to 3 monthly ranibizumab injections of +12 letters (month 3) that continued during observation until month 5 (+ 13.1 letters), followed by a prompt decrease, while change in CRT was similar to ranibizumab alone (gradual increase after cessation of ranibizumab). Patients in our combination group received less laser retreatment at week 8 compared to grid group (7 versus 2). This is most probably due to the lack of oedema caused by ranibizumab treatment. In conclusion, grid treatment did not prevent recurrence of macular oedema. It might prolong time to re-injection considering change in BCVA as retreatment criteria, but not considering change in CRT as retreatment criteria. Our data support a morphology-based

PRN regimen to prevent undertreatment. BRAVO ranibizumab patients received grid rescue in 19.8% (0.5 mg) and 18.7% (0.3 mg) (Campochiaro et al. 2010). Comparison to RABAMES combination group is limited because BRAVO did not report results for subgroups. Tan et al. treated significantly less ranibizumab patients (6.7%) with rescue grid laser and similarly did not report subgroup results (Tan et al. 2013). Given that rescue laser did add to the significant improvements in BCVA by ranibizumab, Tan et al. (2013) concluded that usage of ranibizumab alone would likely be similar to a combination of grid and ranibizumab, supporting our findings.

#### Comparison to other studies

Few other studies investigated anti-VEGF agents (bevacizumab or ranibizumab) alone or in combination versus grid laser photocoagulation in macular oedema secondary to BRVO that uniformly reported superior results for ranibizumab or combination compared to grid treatment (Russo et al. 2009; Salinas-Alamán et al. 2011; Azad et al. 2012). Study results are limited by small sample sizes and variability of patient characteristics (duration and BCVA).

#### Limitation sample size

RABAMES was planned as a proof-of-concept study before estimates for the effect of ranibizumab in BRVO were available. Feasibility was considerably limited regarding our means, number of study sites, relatively rare incidence of significant visual loss due to macular oedema in BRVO and the need for a sensible recruitment period. Tan et al. (2014) performed sample size calculation and aimed at 21 patients per group. Recruitment was terminated after more than 4 years, when 36 patients were randomized. The decision to terminate recruitment was taken when BRAVO results were first published (2011, online in April 2010). At that time, we had randomized 30 patients over a period of 24 months. Results provided consistent estimates for ranibizumab, but neither would it have been suitable to calculate sample size during the course of our study, nor be sensible to elongate recruitment unrealistically.

Overall, our data support the hypothesis that ranibizumab monotherapy is superior to grid laser photocoagulation in BRVO patients with chronic (>3 months) macular oedema who meet the practice guidelines set forth by the Branch Vein Occlusion Study. Grid combined with ranibizumab neither enhanced functional and morphological improvement of ranibizumab nor did it prevent or prolong recurrence of oedema.

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RABAMES Study group (in alphabetical order): Hansjürgen T. Agostini, M.D., Katharina Beinhofer, M.D., Anima Bühler, M.D., Bernd Junker, M.D., Nicolas Feltgen, M.D., Lutz Lothar Hansen, M.D., Lars-Olof Hattenbach, M.D., Christina Korb, M.D., Clemens Lange, M.D., Katrin Lorenz, M.D., Alireza Mirshahi, M.D., Amelie Pielen, M.D., Katharina A. Ponto, M.D, S. G. Priglinger, M.D., Caroline Schäfer, M.D., contributed as participating investigators; Isabella Zwiener, Ph.D. and Felix Jost, Ph.D., performed the statistical tests; Isabel Strübin and Judith Metz provided and cared for study patients.

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## Supporting Information

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

**Table S1.** Best-corrected visual acuity data of individual patients.