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RETINAL DISORDERS

Efficacy and safety of a fixed bimonthly ranibizumab treatment regimen in eyes with neovascular age-related macular degeneration: results from the RABIMO trial

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Abstract
Purpose To evaluate prospectively the efficacy and safety of a fixed bimonthly ranibizumab treatment regimen (RABIMO) in eyes with neovascular age-related macular degeneration (nAMD) and to compare these results with a *pro re nata* (PRN) treatment scheme.
Methods This was a 12-month, phase IV, single center, randomised, non-inferiority study. Following three initial monthly injections, patients were randomised to receive either ranibizumab bimonthly (RABIMO group) or ranibizumab PRN (PRN group) ($n = 20$ each). Main outcome measures were best-corrected visual acuity (BCVA), central retinal thickness (CRT), number of injections, and adverse events (AEs).
Results BCVA [median (interquartile range, IQR)] increased significantly in both groups after 12 months [RABIMO group +8.5 (14); PRN group +6.5 (16) ETDRS letters] when compared to baseline ($p < 0.0001$; $p = 0.0085$). At month 12, the RABIMO treatment regimen was non-inferior to the PRN scheme (ΔBCVA = 3.5 ETDRS letters; $p < 0.0001$). CRT was significantly reduced in both groups after the 12-month study period ($p < 0.0001$ each), with no significant difference between groups ($p = 0.6772$). Number of overall injections [median (IQR)] was 8 (0) in the RABIMO versus 4 (5) in the PRN group ($p = 0.0037$). Three patients in the RABIMO group received one additional unscheduled injection. We observed no significant differences between groups in the number of patients with reported SAEs/AEs (RABIMO group $n = 6/15$; PRN group $n = 7/13$) ($p = 0.7357/p = 0.4902$).
Conclusions We found no evidence of significant functional or anatomical differences between the RABIMO and PRN treatment regimens. However, the RABIMO group's number of injections was twice as high as the PRN group's (protocol-driven). In light of potential side effects, the fixed bimonthly treatment regimen might not be advisable for routine clinical care, but it might be a worthwhile treatment option if monthly monitoring is not possible. Eudra-CT number: 2009-017324-11.

Keywords Age-related macular degeneration · AMD · Ranibizumab · Treatment schedule · PRN · Optical coherence tomography

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Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in industrialised countries in individuals aged 50 years or older [1, 2]. Although the non-neovascular (dry) AMD subtype remains by far the most common variant, the neovascular phenotype is considered responsible for rapid and substantial visual acuity decline. The latter is

characterised by the development of chorioretinal neovascularisation (CNV) [3, 4]. The current standard of care is the intravitreal injection of anti-VEGF substances [5]. Ranibizumab (Lucentis®; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA, USA), is a humanised monoclonal antibody fragment (Fab) approved for the treatment of CNVs due to nAMD in 2006 [6].

The pivotal MARINA and ANCHOR studies explored the efficacy and safety of ranibizumab in the treatment of nAMD by comparing monthly ranibizumab with either sham injections [7] or verteporfin treatment [8] and demonstrated a significantly better VA outcome in the ranibizumab-injected eyes [7, 8]. The MARINA study's results demonstrated a mean best corrected visual acuity (BCVA) gain of 7.2 letters in the ranibizumab as compared with a 10.4 letter loss in the sham-injection group ($p < 0.001$) after 12 months [7]. When comparing patients undergoing ranibizumab injections to those receiving verteporfin therapy [photodynamic therapy (PDT)], the investigators documented a mean increase of 11.3 letters in the ranibizumab-treated eyes, whereas mean BCVA declined by 9.5 letters in the PDT group ($p < 0.001$) after 12 months [8].

Setting up a fixed monthly treatment schedule is challenging in routine clinical care, and even it wasn't, overtreatment would be the consequence for specific patients with nAMD, something that should obviously be avoided [9, 10]. Since completion of the pivotal ranibizumab trials, various strategies have been evaluated to reduce the frequency of injections. The *pro re nata* (PRN) approach entailing an initial phase with three intravitreal injections (upload) followed by injections when needed has attracted particular attention [11–15]: mean BCVA gains between 3.6 and 6.8 letters were reported at 12 months [11–14].

In contrast, a fixed quarterly injection regimen failed to reveal similarly encouraging functional results: the PIER study disclosed a mean BCVA loss of 0.2 letters at 12 months [16]. Nevertheless, a fixed injection schedule would be desirable, as monthly visits accompanied by potential intravitreal injections have proven to be a major burden that created organisational difficulties for both patients and their ophthalmologists. Both therapy schedules lead to obvious under-treatment, which also needs to be avoided [17–19].

The aim of the RABIMO study was to evaluate the efficacy and safety of a fixed bimonthly ranibizumab treatment regimen in eyes with nAMD for the first time, and to compare those results with a PRN treatment scheme.

Material and methods

Study design

RABIMO was a prospective 12-month, two-armed, single center, randomised phase IV clinical trial that enrolled patients with visual impairment due to CNV development in eyes with neovascular AMD. Patients examined in the Department of Ophthalmology, University Medical Center Goettingen, Germany were asked to participate. The study was conducted between April 2010 and August 2013 in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of the University Medical Center Goettingen, Germany. Before entering the study, all patients provided written informed consent to participate following an explicit explanation of the trial's purpose and potential adverse side effects. The RABIMO study is registered with clinicaltrialsregister.eu under Eudra-CT number 2009-017324-11.

Patients

The study cohort consisted of (1) treatment-naïve male and female patients aged ≥ 50 years with visual impairment due to CNV development in eyes with neovascular AMD, (2) patients with BCVA in the study eye of 20/320 to 20/40 according to Early Treatment Diabetic Retinopathy Study (ETDRS) VA testing charts, and (3) a CNV area of ≤ 12 disc diameters.

Key exclusion criteria were: (1) a history of pars-plana vitrectomy or any surgery for nAMD, previous photodynamic therapy (PDT) in the study eye, any focal subfoveal laser treatment or any perifoveal laser treatment within 1 month prior to study start in the study eye; (2) any previous anti-VEGF injection in the study eye; (3) any detachment of the retinal pigment epithelium (RPE) (PED) with a CNV size ≤ 50% of the PED; (4) other ocular diseases (retinal angiomatous proliferation (RAP), presumed ocular histoplasmosis syndrome (POHS), chorioretinal anastomosis (CRA), uveitis, central serous chorioretinopathy (CSC), any CNV for reasons other than nAMD, a tear in the RPE, subretinal bleeding ≥ 50% of the CNV dimensions or ≥ than one a disc diameter, subretinal fibrosis, fibrosis of choroid and/or choriocapillaris, vitreous haemorrhage, dense cataract, full thickness macular hole (FTMH), diabetic retinopathy, myopia ≥ 8dpt, uncontrolled glaucoma with IOP ≥ 30 mmHg under therapy.

Randomisation and treatment/treatment exposure

A randomisation list was produced by a validated system that randomly assigned patients at a 1:1 ratio during the baseline visit into one of two treatment groups: (1) patients received three monthly ranibizumab 0.5 mg intravitreal injections (upload; in months 0, 1, and 2 at visits 1, 2, and 3) followed by fixed bimonthly injections from month 4/visit 6 on until the end of the study at month 12/visit 14 (RABIMO group); if

needed, additional ranibizumab injections could be given beyond the fixed bimonthly regimen; (2) patients received three monthly ranibizumab 0.5 mg intravitreal injections (upload; months 0, 1, and 2 at visits 1, 2, and 3) followed by a PRN treatment regimen from month 3/visit 5 on until the end of the study at month 12/visit 14 (PRN group). All patients in both groups were seen on a monthly basis to be able to decide, (1) if additional injections were needed in the RABIMO group (rescue injection) and (2) when to perform reinjections in the PRN group (Fig. 1). The PRN regimen was conducted in accordance with the Summary of Product Characteristics (SmPC) of ranibizumab at the start of this investigation. Specifically: the criteria for reinjections were a loss of ≥ 6 ETDRS letters and an increase in CRT, as determined via TD-OCT, of ≥ 100 μm.

At visit four, which was scheduled 2 weeks after the end of the loading phase, BCVA and CRT measurements were taken, and we referred to those results during the following visits to decide whether to carry out extra ranibizumab injections [20, 21]. We assumed that at that time point, namely 2 weeks after the initial monthly upload with three injections, ranibizumab is most efficacious. The need for additional ranibizumab injections in both groups was defined as (1) a loss of ≥ 6 ETDRS letters in comparison to visit 4, or (2) an increase in CRT ≥ 100 μm in comparison to visit 4 at each of the follow-up examinations until month 12 (visit 14). If both eyes were eligible, the eye with worse BCVA was included. Neither the treating nor the examining physician was masked in this series.

Study objectives

Our primary objective was to evaluate the impact of the injection frequency on visual acuity development (BCVA after 12 months in comparison to baseline). The secondary objectives were (1) to investigate proportion of patients with a BCVA gain or loss of ≥ 15 letters at month 12 in comparison to baseline; (2) to evaluate anatomical changes in the macula: a. central retinal thickness (CRT) as detected via optical coherence tomography (OCT); b. area of choroidal neovascularisation (CNV) as determined by fluorescein angiography (FAG); c. number of eyes with sub- and intraretinal haemorrhages as evident in color fundus photography (CFP); (3) to describe adverse events; and (4) to analyse the number of additional intravitreal injections needed.

Efficacy and safety assessments

BCVA of the study eye was assessed at each visit by a certified examiner using ETDRS VA testing charts. The standard testing distance was 4 m, which was reduced to 1 m in cases when a patient could not read at least four letters at 4 m.

Color fundus photography (CFP) and fluorescein angiography (FAG): patients underwent both examinations at screening, visit 4, and at the end of the study. CFP and FA images were analysed by two independent investigators separately (HH and NF) using the Zeiss Funduskamera FF450 + IR (Zeiss, Germany).

Optical coherence tomography: TD-OCT (Stratus®, Zeiss, Germany) examinations were conducted at all visits. Central retinal thickness was assessed by automated measurements provided by the Stratus OCT software, which automatically places segmentation lines at the inner retinal boundary (vitreoretinal interface) and the anterior boundary of the retinal pigment epithelium, between which the retinal thickness is measured automatically by the software [22].

Treatment exposure The number of ranibizumab injections administered to each treatment group was evaluated over 12 m.

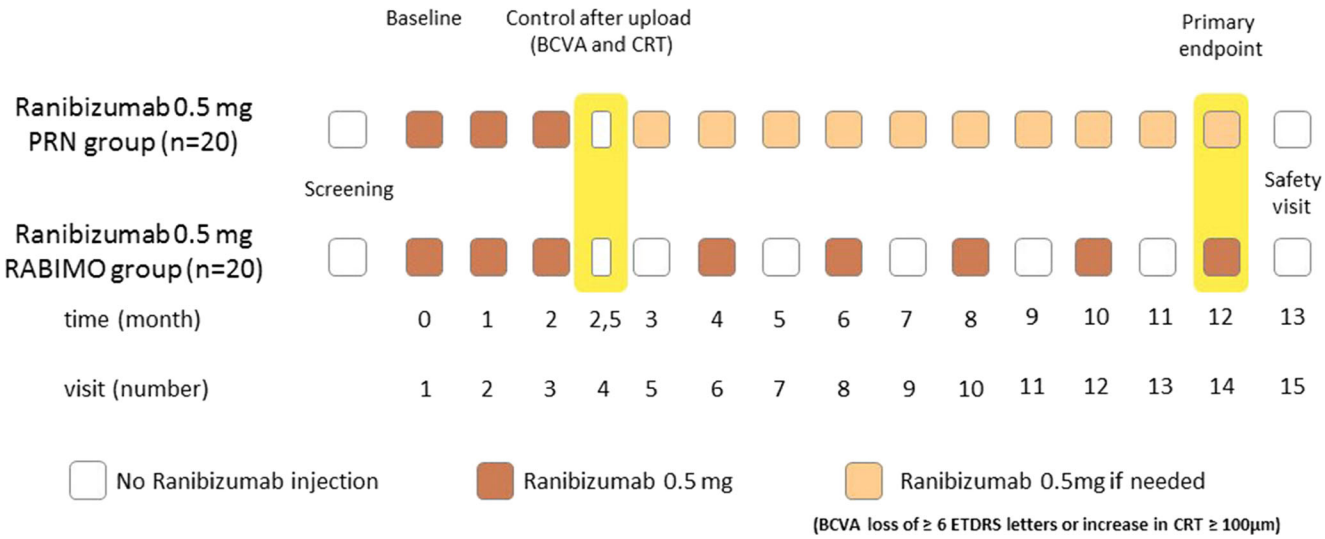

Fig. 1 Treatment schedule

Safety assessments The incidence of ocular and non-ocular adverse events (AEs) and serious adverse events (SAEs) was assessed during the 12-month study period at each visit, as was their possible relationship to the study treatment and/or ocular injection procedure.

Statistical analysis

Primary analysis was carried out on the intention to treat (ITT) set that included all patients (n = 40) who were randomised to one of the two treatment arms [RABIMO group; PRN group (n = 20 each)] and who had completed the upload phase and at least one more visit including BCVA measurement in the maintenance phase. The primary analysis was conducted using the one-sided *t*-test (alpha = 5%) on the ITT. Efficacy was analysed by comparing BCVA development with BCVA baseline values. We noted whether BCVA development in the RABIMO group was ≥ 12 letters worse/less than in the PRN group (null hypothesis) as measured per the differences in number of BCVA letters (ETDRS) at month 12 compared to baseline in the RABIMO treatment versus the PRN treatment regimen. As there was just one primary endpoint, no adjustment was necessary. No further subgroup analysis was performed. We also conducted a sensitivity analysis including all patients treated per the protocol with no missing data (per protocol (PP) data set): 13 RABIMO group patients were analysed, six of whom had to be excluded (four due to protocol deviations and two discontinued participation). In the PRN group, 12 patients were analysed: eight were excluded, one due to protocol violations, two because of incomplete documentation, and five discontinued participation. In all the statistical analyses, we conducted, the ITT and PP data sets were similar. This in turn demonstrates how robust our results are, regardless of the missing values. Because both analyses are consistent, we provide only the ITT data set statistics.

The safety analyses were conducted on the safety set. All patients in each group who had received at least one injection and had at least one post-baseline safety assessment were included ($n = 40$). AEs were summarised by reporting the number and percentage of patients with any ocular and/or non-ocular AEs.

Results

Patient Demographics and Baseline Characteristics

All 40 patients (100%) screened were randomly assigned to one of the following treatment groups: 20 patients (50%) to the RABIMO group and 20 participants (50%) to the PRN group. In all, 18 patients (90%) in the RABIMO group and 15 patients (75%) in the PRN group completed the 12-month study. Main reasons for discontinuation in the RABIMO and PRN groups were death [one patient (5%) and two patients (10%), respectively], AEs [one patient (5%) and two patients (10%), respectively] and consent withdrawal [0 patients (0%) and one patient (5%), respectively] (Fig. 2). Efficacy and safety analyses were conducted on the ITT (overall $n = 40$; RABIMO and PRN group $n = 20$ each) and safety set (overall $n = 40$; RABIMO and PRN group $n = 20$ each), respectively.

Overall, patient demographics and baseline ocular characteristics were similar between the two treatment groups as illustrated in Table 1.

At baseline all patients reported having at least one active concomitant ocular [RABIMO group $n = 11$ (55%); PRN group $n = 13$ (65%) and/or non-ocular (RABIMO group $n = 19$ (95%); PRN group n = 19 (95%)] medical condition, among these were dry and neovascular AMD [RABIMO group n = 8 (40%); PRN group n = 5 (25%)], hypertension [RABIMO group $n = 14$ (70%); PRN group $n = 13$ (65%)], allergies [RABIMO group $n = 4$ (20%); PRN group $n = 1$ (5%)], and skin-related disorders [RABIMO group $n = 1$ (5%); PRN group $n = 3$ (15%)]. Three patients were already pseudophakic in the study eye at baseline (RABIMO group $n = 0$; PRN group $n = 3$).

Efficacy

Best-corrected visual acuity

We observed no significant difference in BCVA [median (interquartile range, IQR)] at baseline between the two groups [RABIMO group 60.5 (17.5) ETDRS letters; PRN group 60.5 (16.5) ETDRS letters] ($p = 0.8465$). The initial monthly upload phase triggered a numerically greater BCVA increase in the RABIMO group [+9.5 (9.5) ETDRS letters] compared to the PRN group [+6 (7) ETDRS letters], although this difference was not statistically significant ($p = 0.3674$). At month 3/visit 4, BCVA in the RABIMO group was 72.5 (22.5) ETDRS letters as compared to 65 (16.5) ETDRS letters in the PRN group ($p = 0.7388$) (Table 2). This initial gain in both groups, and the RABIMO treatment scheme's numerical superiority was maintained until the end of the study at month 12/visit 14 [RABIMO group 75.5 (27.5) ETDRS letters; PRN group 67 (16.5) ETDRS letters] ($p = 0.5958$). The change in BCVA development between baseline and month 12/visit 14 was calculated to be +8.5 (14) ETDRS letters in the RABIMO group and +6.5 (16) ETDRS letters in the PRN group (Δ 3.5 ETDRS letters; $p < 0.0001$). During the maintenance phase, BCVA rose in the RABIMO group by 1.5 (13) ETDRS letters, but fell by 0.5 (8.5) in the PRN treatment group ($p < 0.0001$) (Fig. 3). Therefore, the RABIMO treatment protocol was non-inferior to the PRN treatment scheme (Fig. 4).

At month 12 visit 14, we identified no significant difference between the proportions of patients in both groups who gained ≥ 15 ETDRS letters during the study phase [six

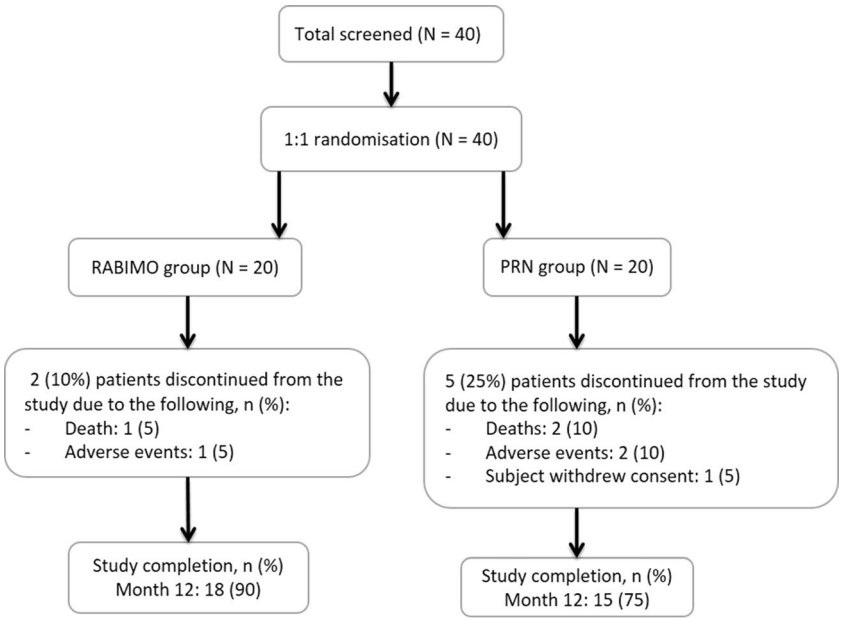

Fig. 2 Patient Disposition (Randomised Set)

RABIMO group patients (30%); eight PRN group patients (40%); $p = 0.5073$) or lost (two RABIMO group patients (10%); one PRN group patient (5%); $p = 0.5483$).

Anatomical outcomes

Both groups demonstrated a significant CRT reduction within the 12-month treatment period ($p < 0.0001$) with no significant difference between groups ($p = 0.6772$). CRT in the RABIMO group [median (interquartile range, IQR)] [370 μm (92 μm)] was lower at baseline than in the PRN group [428 μm (183 μm)] ($p = 0.0621$). Both groups' CRT decreased substantially afterwards from month 1/visit 2 on [RABIMO group 241 μm (41 μm); PRN group 239 μm (44 μm)]. This reduction was maintained till the study's conclusion at month 12/visit 14 [RABIMO group 247 μm (80 μm); PRN group 230 μm (69 μm)]. There was no significant group difference in CRT measurements at month 3/visit 4 [RABIMO group 227 μm (42 μm); PRN group 225 μm (64 μm); ($p = 0.73$]70) (Table 2).

Active CNV size [median (interquartile range, IQR)] at baseline in both groups was similar [RABIMO group 2.33 mm^2 (1.66 mm^2); PRN group 2.42 mm^2 (2.61 mm^2)] ($p = 0.4144$), falling substantially in both groups until month 3 visit 4 [RABIMO group 0 mm^2 (0 mm^2); PRN group 0 mm^2 (0.15 mm^2)] ($p = 0.8976$). This reduction was maintained until the end of the study [RABIMO group 0 mm^2 (1.48 mm^2); PRN group 0 mm^2 (0.15 mm^2)] ($p < 0.0001$) with no group differences (p = 0.9455).

Sub- and/or intraretinal haemorrhages were equally evident in both treatment groups at baseline (RABIMO group 12 eyes, 60%; PRN group 13 patients, 65%) ($p = 0.7440$). After 4 months of treatment, the number of eyes with intra- and/or subretinal bleeding had fallen to four patients (20%) in the RABIMO group and six (30%) in the PRN group; after 12 months, this reduction continued in another five patients

Table 1 Baseline patient demographics and ocular disease characteristics

Characteristics	RABIMO group (n = 20)	PRN group (n = 20)	Total (n = 40)	Differences between groups (p value)
Median age (IQR), years	79 (9)	81 (12)	79 (12)	0.1118
Gender, n (%)				0.5073
Male	6 (30)	8 (40)	14 (35)	
Female	14 (70)	12 (60)	26 (65)	
Median baseline BCVA (IQR), letters	60.5 (17.5)	60.5 (16.5)	60.5 (17)	0.8465
Median baseline CRT (IQR), μm	370 μm (92 μm)	428 μm (183 μm)	396 μm (136 μm)	0.0621
Median active CNV area (IQR), mm^2	2.3 mm^2 (1.7 mm^2)	2.4 mm^2 (2.6 mm^2)	2.3 mm^2 (1.8 mm^2)	0.4144
Subretinal and intraretinal bleeding, n (%)	12 (60);	13 (65)	25 (62.5)	0.7440

Table 2 Best corrected visual acuity and central retinal thickness at month 3/visit 4

Characteristics	RABIMO group (n = 20)	PRN group (n = 20)	Differences between groups (p value)
Median BCVA (IQR), letters	72.5 (22.5)	65 (16.5)	0.7388
Median change BCVA (IQR) since baseline, letters	+9.5 (9.5)	+6 (7)	0.3674
Median CRT (IQR), μm	227 μm (42 μm)	225 μm (64 μm)	0.7370

(25%) and one patient (5%), respectively, with no group differences ($p = 0.7164$ and $p = 0.1818$).

Number of injections

The number of injections [median (interquartile range, IQR)] in the RABIMO group was eight, whereas the PRN group underwent just four (five) intravitreal ranibizumab injections ($p = 0.0031$). Eight patients in the PRN group needed only the three-monthly upload injections and no further treatment within the 12-month study period. Three patients in the RABIMO group were given an additional injection between the routinely scheduled bimonthly injections (Fig. 5).

Safety

Serious adverse events (SAEs): no ocular SAEs in the study eye were reported. Four SAEs were reported in the fellow eye [newly-diagnosed nAMD ($n = 3$), one of these accompanied by a macular haemorrhage; worsening infectious keratitis ($n = 1$)]. Non-ocular SAEs were reported in six RABIMO-group patients (30%) and in seven PRN-group patients (35%). In the RABIMO group one patient (5%) died due to stroke and in the PRN group two patients (10%) died, one due to sudden cardiac arrest and the second participant as a consequence of severe sepsis. None of the ocular and non-ocular SAEs was suspected of being related to the study drug or injection procedure (table 3). There was no significant difference between groups regarding patients with any SAE ($p = 0.7357$).

Adverse events (AEs): Overall 35 AEs were reported in 15 patients assigned to the RABIMO group and 30 AEs were reported in 13 patients randomised to the PRN group ($p = 0.4902$). Ocular AEs in the study eye were reported in 11 RABIMO-group patients and in four PRN-group patients. Non-ocular AEs were documented in 13 patients in the RABIMO and in ten patients in the PRN treatment group. The most frequent AEs are summarised in Table 4. There was no significant group difference regarding patients with any AE ($p = 0.4902$).

Discussion

RABIMO is, to the best of our knowledge, the first prospective and randomised trial investigating the clinical efficacy and safety of a bimonthly ranibizumab treatment regimen in eyes with nAMD over 12 months and comparing these results with the standard of care, the *pro re nata* injection scheme (PubMed search on 2016/06/26). A recently published

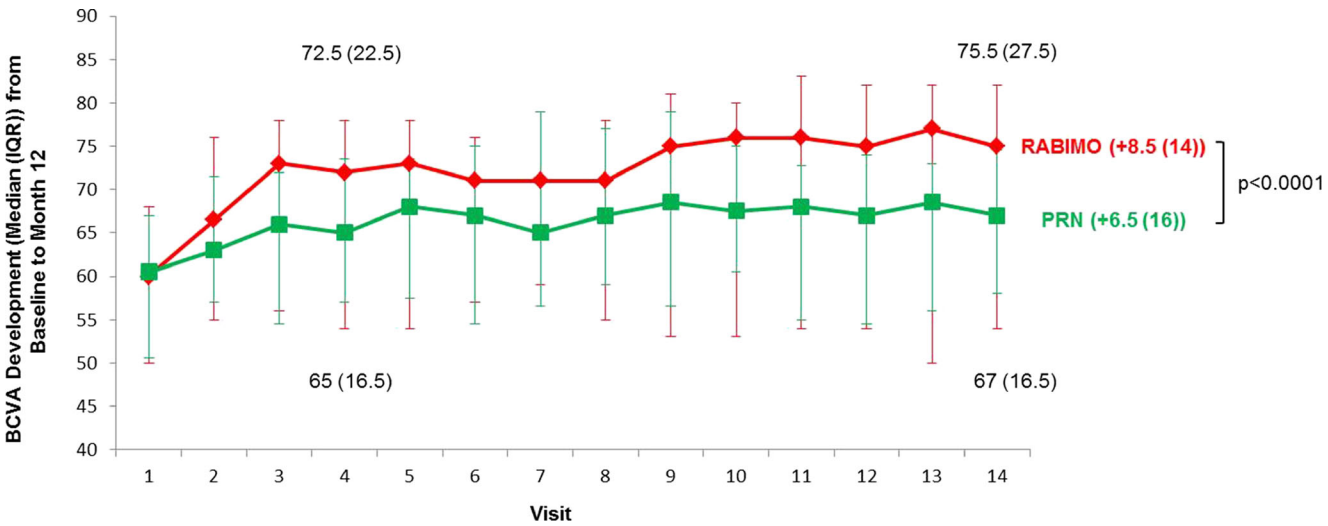

Fig. 3 Median (IQR) BCVA Development from Baseline to Month 12 (ITT Set [Last Observation Carried Forward])

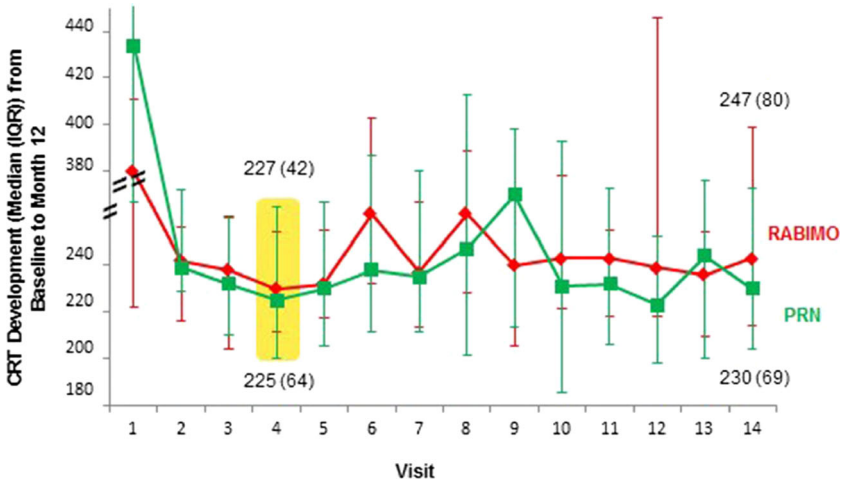

Fig. 4 Median (IQR) CRT Development from Baseline to Month 12 (ITT Set [Last Observation Carried Forward])

retrospective analysis detected "satisfactory visual results" following a bimonthly ranibizumab treatment schedule [20] and another prospective trial without an initial upload phase [21] demonstrated significant functional and anatomical improvements. However, neither of those investigations had a control group.

In this investigation, BCVA rose during the first 3 months in both groups, with the RABIMO group exhibiting numerical, but not statistical superiority. The RABIMO scheme's superiority accompanied by their flatter CRT at baseline might reflect milder disease activity than in eyes randomised to the PRN group. On the other hand, eyes with a thicker CRT at baseline could benefit more from anti-VEGF injections. Ultimately, these questions remain unanswered, and the RABIMO group's numerical superiority can most likely be attributed to the small number of patients enrolled in both groups. This initial BCVA gain was maintained in both groups until the end of the study. The RABIMO treatment regimen was non-inferior to the PRN scheme. Both strategies thus turned out to be effective in the treatment of eyes with nAMD.

Comparing this trial's results with BCVA outcomes in the pivotal ranibizumab trials, it becomes obvious that eyes

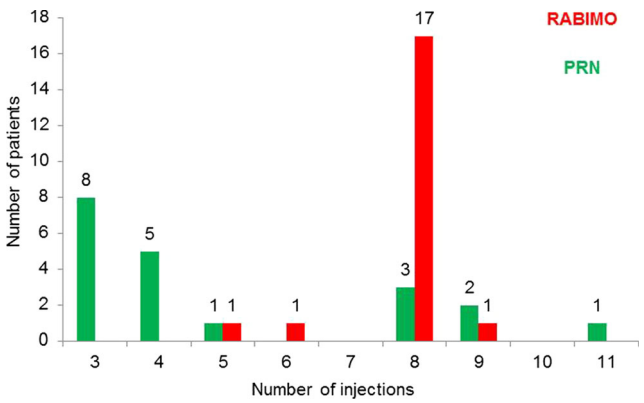

Fig. 5 Number of injections administered during the 12-month study period

treated according to the PRN scheme [+6.5 (IQR: 16) ETDRS letters)] yielded results similar to those in the CATT [23] or MARINA study [7], whereas eyes injected according to the RABIMO scheme [8.5 (14) ETDRS letters)] displayed BCVA gains comparable to the ANCHOR trial's [8] (Table 5; Fig. 6).

Sawada and colleagues investigated the efficacy of at least three bimonthly intravitreal ranibizumab injections in 30 eyes with nAMD and polypoidal choroidal vasculopathy (PCV) in a prospective interventional case series. After 12 months, BCVA increased and CRT decreased significantly as both did equivalently in our series. As in their study design contrary to ours no loading doses were foreseen, overall six injections within the 1-year study period were planned. Nine of the 30 patients included received the planned six injections, whereas 21 patients needed fewer injections. The limitation of this investigation by Sawada et al. is the missing PRN-driven control group [21]. Warwick and coworkers retrospectively investigated the real life clinical outcome of 165 poorly responsive and treatment-naïve patients with nAMD who were treated with a bimonthly aflibercept treatment regimen. Both, treatment naïve, as well as switched patients from bevacizumab or ranibizumab, who poorly responded, received three monthly injections followed by a fixed bimonthly treatment schedule. The authors concluded that a fixed bimonthly injection schedule is effective in both types of patients with a significant better functional and anatomical outcome in treatment naïve patients. In contrast to our investigation, clinical visits were scheduled only bimonthly and thus undertreatment might have occur. In regard to numbers of injections within the 1-year study, Warwick reported about 7.1 injections in treatment naïve, as well as about 7.5 applications in switched patients, both of which are somewhat lower in comparison to overall eight injections that were administered in the RABIMO trial [24]. Cohen et al. reported in a retrospective investigation with 27 treatment naïve eyes included about a bimonthly fixed ranibizumab regimen after an initial loading period with three

Table 3 Ocular (study eye and fellow eye) and non-ocular serious adverse events from baseline to month 12 (safety set*)

	RABIMO group (n = 20) N (%)	PRN group (n = 20) N (%)	Total (n = 40) N (%)
Patients with ocular SAEs (study eye), total	0 (0)	0 (0)	0 (0)
Patients with ocular SAEs (fellow eye), total	0 (0)	4 (20)	4 (10)
nAMD	0 (0)	3 (15)	3 (8)
Infectious keratitis	0 (0)	1 (5)	1 (3)
Patients with non-ocular SAEs, total	6 (30)	7 (35)	13 (33)
Number of non-ocular SAEs, total	7 (35)	10 (50)	17 (43)
Death	1 (5)	2 (10)	3 (8)
Fall/pelvic fracture	1 (5)	0 (0)	1 (3)
Heart rhythm disorder	1 (5)	0 (0)	1 (3)
Transient ischaemic attack	1 (5)	0 (0)	1 (3)
Stroke	1 (5)	0 (0)	1 (3)
Hypertension	1 (5)	0 (0)	1 (3)
Abdominal aortic aneurysm	1 (5)	0 (0)	1 (3)
Severe infection	1 (5)	0 (0)	1 (3)
Hodgkin's disease relapse	0 (0)	2 (10)	2 (5)
Spondylodiscitis	0 (0)	1 (5)	1 (3)
Peripheral arterial disease	0 (0)	2 (10)	2 (5)
Diarrhoea	0 (0)	1 (5)	1 (3)
Knee infection	0 (0)	1 (5)	1 (3)
Syncope	0 (0)	1 (5)	1 (3)

* Comprises all randomised patients who received at least one ranibizumab injection and underwent at least one post-baseline safety assessment. Patients with multiple SAEs associated with the same disease entity are only counted once in each group

monthly injections. Mean visual gain was about 8.4 letters with a mean number of 8.77 injections. Compared to our data with a median of 9.5 letters improvement and a median of eight injections given, BCVA increase was lower with slightly more injections [20]. As in our investigation, examinations were performed every 4 weeks to avoid an undertreatment.

Table 4 Most frequent ocular and non-ocular adverse events from baseline to month 12 (safety set*)

	RABIMO group (n = 20) N (%)	PRN group (n = 20) N (%)	Total (n = 40) N (%)
Blepharitis	3 (15)	2 (10)	5 (13)
Vitreous floaters	3 (15)	0 (0)	3 (8)
RPE defects	2 (10)	1 (5)	3 (8)
nAMD fellow eye	1 (5)	3 (15)	4 (10)
Hyposphagma	1 (5)	2 (10)	3 (8)
Hypertension	1 (5)	1 (5)	2 (5)
Heart rhythm disorder	0 (0)	1 (5)	1 (3)

* Comprises all randomised patients who received at least one ranibizumab injection into the study eye and underwent at least one post-baseline safety assessment. Patients with multiple SAEs associated with the same disease entity are only counted once in each group

Like in the study by Sawada et al., no PRN control group was included in the series by Cohen and colleagues. Finally, the VIEW data published by Heier et al. showed an overall increase in BCVA in the $2q^8$ aflibercept arm of 8.4 letters and it was, therefore, slightly lower compared to our data [25]. This comparison must be made with reservations, because the two trials' results cannot be compared directly. These results might suggest, however, that both substances are similarly efficacious within the same treatment regimen. A prospective head-to-head study should be conducted to address this open question. In summary, it remains challenging to compare our RABIMO group's results with others in the literature though, because we are the first to have administered this particular ranibizumab-injection regimen with a second baseline 2 weeks after the loading phase as a new basis to route reinjections in either group.

No group differences were detected concerning eyes gaining or losing ≥ 15 ETDRS letters, again demonstrating the RABIMO treatment strategy's non-inferiority. The present study's RABIMO and PRN groups' results concur with earlier trials' findings in terms of the numbers of patients who gained more than 15 letters (see Table 5).

Another novelty of the RABIMO study is the additional visit (visit 4) 2 weeks after the completed loading phase. The

Table 5 Comparison of RABIMO results with pivotal ranibizumab and aflibercept trials in the treatment of nAMD-affected eyes

Trial	ANCHOR [8]	MARINA [7]	PIER [16]	CATT [23]	VIEW 1&2 [24]	RABIMO (RABIMO/PRN)
Number of eyes (n)	140	240	61	298	616	40
Age (years)	76	77	78	78.4	75.8	79
BCVA (ETDRS letters)	47	53.7	53.7	61.5	53.6	60.5
Additional visit after upload	no	no	no	no	no	yes
Follow-up (month)	12	12 (24)	12	12	12 (24)	12
BCVA gain after upload	9.8	5.9	5	5.6	7.5	9.5/6.0
BCVA gain at month 12	11.3	7.2	−1.6	6.8	8.5	8.5/6.5
BCVA gain ≥ 15 ETDRS letters (%)	40.3	33.8	13.1	25	31	30/40
Number of injections (n)	12	12 (24)	6	6.9	7.5	8/4

anti-VEGF effect is assumed to be maximum at this time point. This visit was defined as the maintenance phase's baseline for deciding whether or not to reinject in the PRN treatment group. It is interesting to observe that BCVA development [median (IQR)] in the RABIMO group [1.5 (13) ETDRS letters] was significantly better via this approach than in the PRN group [-0.5 (8.5) ETDRS letters] ($p < 0.0001$), whose BCVA in fact worsened. We thus maintain that such an additional visit might serve as a clinical detector for imminent under-treatment when carrying out a PRN treatment regimen in the future; under-treatment we can assume here as the PRN arm received only four of five injections. This extra visit could enable us to more readily and accurately measure a marginal loss of BCVA than the current visit schedule, namely by comparing the patient's actual BCVA with that at baseline or at the visit a month after the upload phase. Nevertheless, more research is necessary to prove this hypothesis.

BCVA improvements were accompanied by specific anatomical changes. CRT, active CNV size, as well as sub- and/or intraretinal bleedings were reduced after 12 months in both groups without significant group differences. Again, the RABIMO treatment was non-inferior to PRN. Both groups exhibited a distinct reduction in CRT values until visit 4. A zig-zag course was noted in the RABIMO group between visits 5 and 9 that was not evident during the later study course. In contrast, such zig-zag variations in CRT values became apparent during the entire maintenance phase in the VIEW studies administering bimonthly intravitreal aflibercept to treat eyes with nAMD [25]. This discrepancy remains unresolved. CRT fluctuations in our PRN treatment group

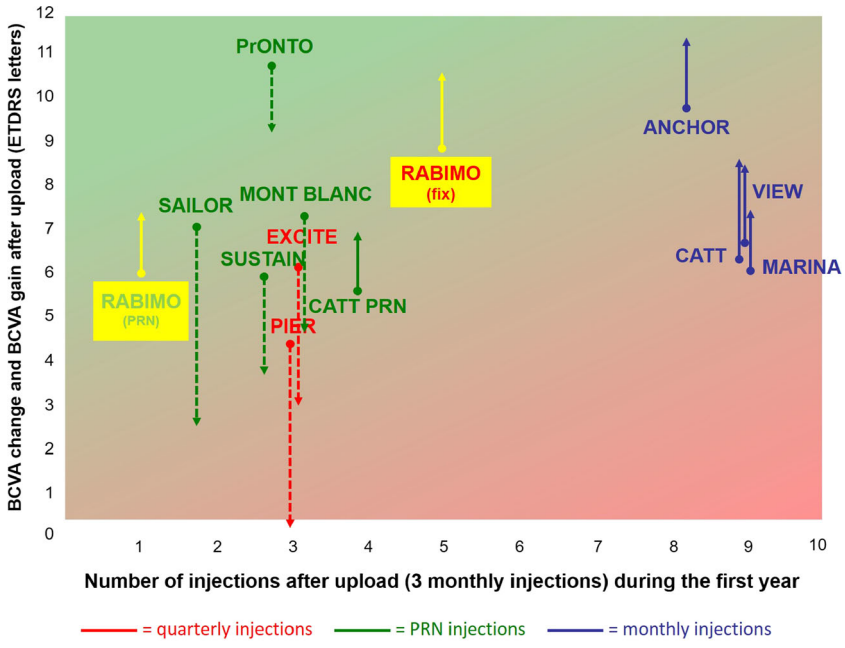

Fig. 6 Comparison of BCVA treatment effects between RABIMO and pivotal ranibizumab and aflibercept trials (adapted from [26] with permission)

appear quite pronounced in comparison to CRT findings in the pivotal trials [23]. This too might be attributable to the low number of eyes in our trial.

The number of intravitreal injections [median (IQR)] in our RABIMO group [8 (0)] was twice as high as that in the PRN treatment group [4 (5)] ($p = 0.0031$). In the PRN group, only eight patients needed upload injections, whereas three patients in the RABIMO group were given one additional injection each. These rescue injections could be very important to ensure good treatment results when following a fixed bimonthly regimen and were also performed in previous investigations [20, 21]. In summary, the data demonstrates the wide variability in eyes in need for anti-VEGF treatment and might reflect under-treatment in the PRN group as well. Regular visits including OCT examinations are necessary to ascertain the optimum treatment strategy for each patient (e.g. PRN, T&E) [27]. Such an approach would minimise procedure-related risks (e.g. endophthalmitis) [28] and help prevent over-treatment (e.g., geographic atrophy [10], growing tolerance [29]). In this respect, PRN seems to be superior to a RABIMO treatment regimen. Comparing our numbers of PRN injections (four) with those of previous trials (6–7.5) [16, 23, 25] it is evident that we carried out fewer injections. We do not know whether our inclusion criteria, small group sizes, a selection of very good responders, the use of reinjection criteria at visit 4, or a combination thereof is responsible for this observation. As the SmPC of ranibizumab has changed since the RABIMO trial started, the PRN regimen nowadays would probably call for more injections.

No new safety risks were identified in the RABIMO trial [7, 8, 15, 23]. Furthermore, there were no significant differences in SAE and AE reports between groups, although serious cardiovascular events seemed to be more frequent in the RABIMO group. Two patients died in the PRN treatment group, one due to sudden cardiac arrest and the second due to sepsis, a percentage higher than previously described [30]. However, as both events occurred more than 60 days after the last ranibizumab injection, no causal relationship with ranibizumab was suspected. The relatively low number of patients included in this trial might be the reason for both observations. All in all, the safety data from the ranibizumab registration trials [7, 8], from head-to-head trials with bevacizumab [23], as well as from the aflibercept registration trials [25] reveal that the risk for SAE and AE occurrence is not increased in association with ranibizumab [30] and no new safety concerns were identified herein.

The main limitations of the RABIMO trial are the low number of patients included in both groups, the fact that treating and examining physicians were not masked to randomisation, and the use of a TD-OCT device. A subsequent evaluation with a larger patient cohort, blinded medical staff, and an SD-OCT device is now indicated. However, the strengths of our study are its prospective and randomised design, assessment of a never-before prospectively and PRN-controlled described fixed, bimonthly ranibizumab injection scheme in eyes with nAMD, and the implementation of an additional visit 2 weeks after completion of the upload phase, which might function as a clinical detector to avoid under-treatment in the future.

In conclusion, results from the RABIMO trial demonstrate the non-inferiority of a fixed-bimonthly ranibizumab treatment regimen to the standard-of-care, that is, a PRN treatment scheme in eyes with nAMD—a regimen non-inferior in either functional or anatomical aspects or regarding safety. Comparing the results and injection frequencies between the RABIMO and PRN groups suggests that a fixed treatment schedule is generally not necessary, but it could be an option for certain patients if monthly monitoring is not possible. Treating nAMD-affected eyes on a bimonthly basis, following an initial upload phase, entailing a total of eight intravitreal injections within the first year could serve as a kind of upper limit concerning the number of injections needed, an observation supported by other ranibizumab PRN [14], as well as aflibercept fixed-dose [25] trials.

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Compliance with ethical standards

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Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent "Informed consent was obtained from all individual participants included in the study."

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