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Two different treatment regimens of ranibizumab 0.5 mg for neovascular age-related macular degeneration with or without polypoidal choroidal vasculopathy in Chinese patients: results from the Phase IV, randomized, DRAGON study

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ABSTRACT.

Purpose: **To evaluate the efficacy and safety of monthly and *pro re nata* (PRN, guided by visual acuity stabilization and disease activity criteria) ranibizumab regimens in Chinese patients with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV).**

Methods: **This double-masked study randomized nAMD patients (1:1) to ranibizumab monthly from baseline to Month (M) 11 to a PRN regimen from M12 to M23 (monthly group, *n* = 167) versus ranibizumab three monthly doses followed by a PRN regimen up to M23 (PRN group, *n* = 166). Subgroups were assessed based on the presence/absence of PCV (indicated by indocyanine green angiography).**

Results: **Of 334 randomized patients, 41.7% had PCV at baseline. Mean average best-corrected visual acuity (BCVA) change from M3 to M4 through M12 was 3.3 letters with monthly and 1.7 letters with PRN (mean difference: 1.6; 95% CI: −2.95, −0.20, primary end-point). Mean change in BCVA from baseline (monthly/PRN, 53.8/53.7) to M12 and M24 was 12.3 and 11.3 letters in monthly and 9.6 and 9.3 letters in PRN group. Corresponding values for patients with PCV/without PCV were 12.7/12.1 letters (M12) and 12.3/10.6 letters (M24) in monthly and 9.4/9.4 letters (M12) and 9.7/8.7 letters (M24) in PRN groups. The mean number of injections was 11.4 (monthly) and 8.2 (PRN) from Day 1 to M11 and 4.8 (monthly) and 5.0 (PRN) from M12 to M23. No new safety findings were reported.**

Conclusions: **The study results support the use of either ranibizumab monthly or PRN regimens in Chinese patients with nAMD, regardless of presence of PCV.**

Key words: age-related macular degeneration – monthly regimen – polypoidal choroidal vasculopathy – *pro re nata* regimen – ranibizumab

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Introduction

Neovascular age-related macular degeneration (nAMD) is one of the leading causes of blindness in the elderly population (Wong et al. 2014). In China, nAMD accounts for approximately 10% of cases of blindness (Tang et al. 2015). Polypoidal choroidal vasculopathy (PCV), a variant of type I subretinal neovascularization, is highly prevalent (22.3–61.6%) in Asian patients with presumed nAMD (Wong et al. 2016; Kokame et al. 2019). This necessitates the identification of effective treatment options that can help preserve vision and reduce disease burden in patients with nAMD and those diagnosed with PCV (Hsu et al. 2004; Wong et al. 2014).

Anti-vascular endothelial growth factors (anti-VEGFs) are the established standard of care for the treatment of patients with nAMD. Scientific evidence from randomized clinical trials has shown that ranibizumab (Lucentis®; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA, USA), an anti-VEGF, is effective and well tolerated in treating patients with nAMD (Rosenfeld et al. 2006; Brown et al. 2009). Results from pivotal trials showed that monthly injections of ranibizumab over 2 years substantially improved vision in patients with nAMD (ANCHOR, +10.7 letters; MARINA, +6.6 letters) (Rosenfeld et al. 2006; Brown et al. 2009). However, a monthly regimen may be a treatment burden to both patients and caregivers, and could affect patient compliance (Chen & Han 2012). Data from the SUSTAIN and EXCITE studies suggest that >40% of patients could be over-treated when on a monthly regimen (Holz et al. 2011; Schmidt-Erfurth et al. 2011). Individualized treatment regimens therefore aim at maintaining vision in these patients with fewer injections. The CATT, HARBOR and PrONTO studies showed that a *pro re nata* (PRN) regimen, where treatment is only given as required, results in favourable visual outcomes and requires fewer injections (mean number of injections, 9.9–13.3 over 2 years) compared with monthly treatment (Lalwani et al. 2009; CATT Research Group et al. 2011; CATT Research Group et al. 2012; Busbee et al. 2013; Ho et al. 2014). In Chinese patients, the efficacy and safety of a monthly ranibizumab regimen was evaluated for the treatment of nAMD in the EXTEND II study; results showed that the monthly regimen was effective in improving best-corrected visual acuity (BCVA) and was well tolerated in this population (Zhao et al. 2014). However, the efficacy and safety of the ranibizumab PRN regimen for nAMD in the Chinese population was not investigated.

Ranibizumab and verteporfin photodynamic therapy (PDT; Visudyne®; Novartis AG, Switzerland; verteporfin PDT) have been effective in the regression of polyps and improvement of vision in Asian patients with PCV (Koh et al. 2012; Oishi et al. 2013; Gomi et al. 2015; Koh et al. 2017; Chen et al. 2018). Similarly, aflibercept 2 mg (Eylea®, Regeneron Pharmaceutical Inc., Tarrytown, NY, USA and Bayer Healthcare, Leverkusen, Germany), brolucizumab 6 mg (Beovu®; Novartis Pharma AG) and laser therapy have resulted in a gain or stability of vision in patients with PCV (Gemmy Cheung et al. 2013; Wong et al. 2019). However, an optimal treatment approach for PCV remains to be confirmed.

Thus, the DRAGON study was conducted to evaluate the efficacy and safety of ranibizumab 0.5 mg administered as either monthly (Year 1) followed by PRN [guided by visual acuity (VA) stabilization and disease activity criterion] in Year 2 or initial three monthly doses followed by PRN up to Year 2 in Chinese patients with nAMD. This study also explored the efficacy of ranibizumab based on the presence or absence of PCV at baseline.

Materials and Methods

Study design

DRAGON was a 2-year, double-masked, controlled, multicentre study conducted across 23 centres in China from 22 February 2013 to 23 November 2015. The study was approved by the independent ethics committee or institutional review board of each study centre and was conducted in accordance with the Declaration of Helsinki (2008; 2013) and International Conference on Harmonization Good Clinical Practice guidelines (E6-R1). Patients provided written informed consent before participating in the study. The study is registered with clinicaltrials.gov, NCT01775124.

Treatment-naïve Chinese patients aged ≥50 years with visual impairment due to active choroidal neovascularization (CNV), secondary to AMD with a BCVA Early Treatment Diabetic Retinopathy (ETDRS) Study letter score (at both screening and baseline) between 23 and 78 using ETDRS charts at 4 m (approximately 20/32 to 20/320 Snellen equivalent), were eligible to participate.

Randomization, treatment and masking

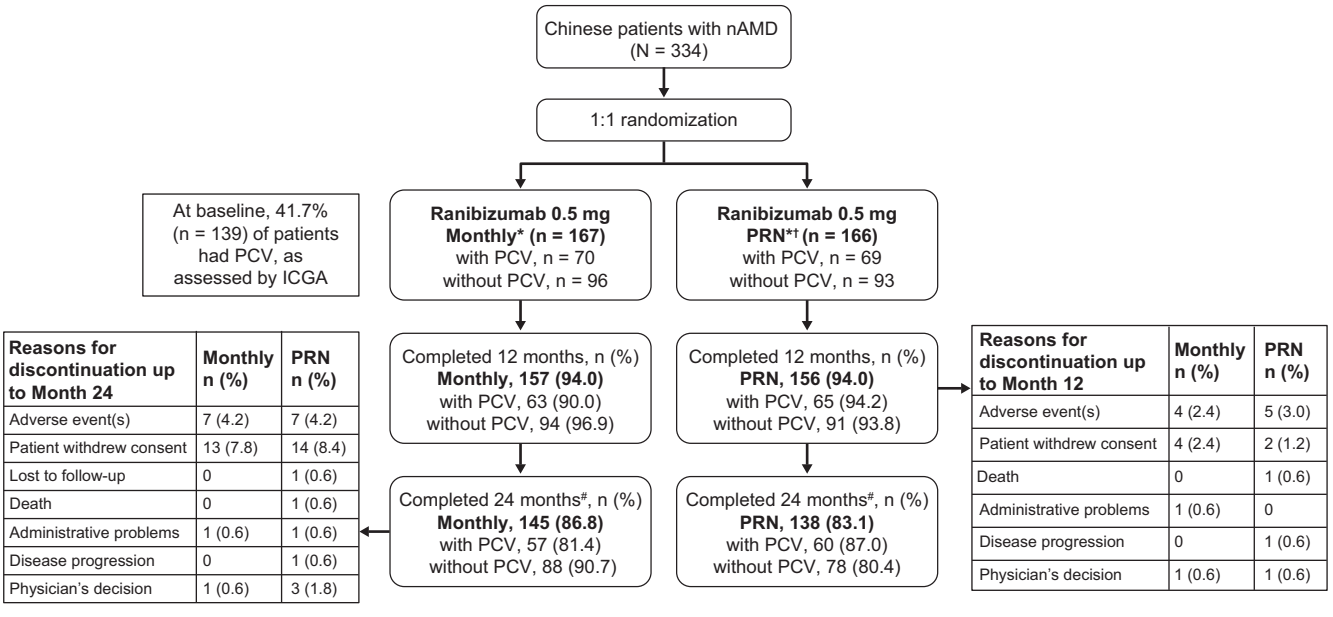
Eligible patients with nAMD (as determined by the investigator) were randomized 1:1 to receive ranibizumab 0.5 mg as per one of the two dosing regimens: (1) monthly from Day 1 to Month 11 (the core treatment period), followed by a PRN regimen from months 12 to 23 (the extension treatment period), or (2) three consecutive monthly injections followed by a PRN regimen up to Month 23 (Fig. 1).

In the PRN regimen, treatment was initiated with monthly injections until maximum VA was achieved; that is, the patient's VA was stable for three consecutive visits, followed by monthly monitoring visits. Treatment was resumed when any loss of VA and/or nAMD progression was indicated by the investigator based on VA, and clinical and anatomical [spectral domain-optical coherence tomography (SD-OCT), or fluorescein angiography (FA)] assessments.

Interactive Response Technology was used to randomize all eligible patients to one of the treatment arms. The VA assessor, evaluating investigator/site staff and patients were masked to the treatment regimen from randomization until database unlock. The treating investigator was unmasked to the treatment assignment and performed the treatments but was not involved in any other aspects of the study. Randomization was stratified based on the presence or absence of PCV at baseline, as determined by the central reading centre (CRC; Bern Photographic Reading Center) after assessing the indocyanine green angiography (ICGA) images obtained during the screening process.

Study objectives

The primary objective was to evaluate the difference in efficacy of a monthly



Reasons for discontinuation up to Month 24	Monthly n (%)	PRN n (%)
Adverse event(s)	7 (4.2)	7 (4.2)
Patient withdrew consent	13 (7.8)	14 (8.4)
Lost to follow-up	0	1 (0.6)
Death	0	1 (0.6)
Administrative problems	1 (0.6)	1 (0.6)
Disease progression	0	1 (0.6)
Physician's decision	1 (0.6)	3 (1.8)

Reasons for discontinuation up to Month 12	Monthly n (%)	PRN n (%)
Adverse event(s)	4 (2.4)	5 (3.0)
Patient withdrew consent	4 (2.4)	2 (1.2)
Death	0	1 (0.6)
Administrative problems	1 (0.6)	0
Disease progression	0	1 (0.6)
Physician's decision	1 (0.6)	1 (0.6)

Fig. 1. Study design and patient disposition. The FAS was used for patient disposition. *One patient in the monthly group (n = 168) was mis-randomized and was excluded from analysis; hence, the monthly group included 167 patients. #Patients from both treatment groups received PRN regimen from Month 12 to study completion. †PRN treatment was guided by visual acuity stabilization criteria. The FAS included all randomized patients to whom study treatment was assigned. FAS = full analysis set, n = number of patients, N = total number of patients, nAMD = neovascular age-related macular degeneration, PCV = polypoidal choroidal vasculopathy, PRN = *pro re nata*.

versus PRN regimen (driven by VA stability and disease activity criteria as judged by the investigator) of ranibizumab 0.5 mg in stabilizing BCVA. Visual acuity (VA) stabilization was defined as stable BCVA for three consecutive monthly assessments performed while on ranibizumab treatment.

The primary efficacy variable was BCVA change averaged from Month 4 through Month 12 (compared with Month 3), which was during the time the treatment regimens differed between the two arms. The average change in BCVA values was calculated for each patient based on the VA at the monthly assessments at Month 4, up to Month 12, after which the mean (including all patients) was calculated and compared with Month 3. This mean average change over time allowed an evaluation of the comparability of the end-point over the period when the treatment regimens differed, providing a robust value of BCVA change.

The secondary objectives were to evaluate the efficacy of a ranibizumab 0.5 mg monthly versus a PRN regimen as assessed by the following: (1) mean BCVA change from Month 1 to Month 24 compared to baseline; (2) BCVA improvement of ≥5, ≥10, ≥15 and ≥30 ETDRS letters from baseline; (3) BCVA loss of <15 ETDRS letters from baseline, at each visit; (4) VA score of ≥73 ETDRS letters at months 12 and 24; (5) change in central subfield thickness (CSFT) from baseline to months 12 and 24; and (6) duration of treatment-free intervals of two treatment groups over the months 12 and 24. Safety of ranibizumab 0.5 mg was assessed over 24 months.

An exploratory objective was to assess the effect of lesion type (i.e. presence or absence of PCV) on the efficacy of ranibizumab. Except for the assessment of change in BCVA and CSFT by lesion type, all analyses were *post hoc*. The efficacy of ranibizumab 0.5 mg was evaluated in subgroups of patients with or without PCV in the monthly and PRN groups, and was assessed by the following: (1) mean BCVA change over time from baseline to months 1 and 24; (2) a BCVA improvement of ≥5, ≥10 and ≥15 ETDRS letters from baseline to months 12 and 24; (3) a BCVA loss of <5, <10 and <15 ETDRS letters from baseline to months 12 and 24; (4) the proportion of patients with BCVA scores ≥69 ETDRS letters at baseline and months 12 and 24; (5) the mean change in CSFT from baseline to months 12 and 24 and; and (6) the proportion of patients with dry retina at baseline and months 12 and 24.

Assessments

Best-corrected visual acuity (BCVA) assessments for the study eye were performed at screening, baseline (Day 1), as well as at monthly visits (defined as every 30 days from baseline) ±7 days to allow for flexibility in scheduling until Month 24. Best-corrected visual acuity (BCVA) was assessed in the sitting position using ETDRS VA testing charts at a starting distance of 4 m. Early Treatment Diabetic Retinopathy (ETDRS) charts included high-contrast Sloan letters (or numbers, or other symbols) in each of 14 lines, lines of equal difficulty, and a geometric progression of letter/number size from line to line. Best-corrected visual acuity (BCVA) was also evaluated for the fellow eye at select visits.

Indocyanine green angiography (ICGA) was performed at screening, SD-OCT was performed at monthly visits, and colour fundus (CF) photography and FA were performed at screening and months 6, 12, 18 and 24. The images were read by the CRC (details are provided in supporting information, Appendix 1). Evidence of CNV was assessed using FA/CF.

Dry retina, defined as a retina with no subretinal fluid, cysts, or intraretinal oedema, was assessed using SD-OCT.

Safety was assessed by incidence, frequency, and severity of adverse events (AEs) and serious AEs (SAEs), irrespective of their relationship to the study drug and/or injection, over the 24-month study period.

Statistics

Sample size calculation

The difference between treatment regimens for the primary efficacy variable was hypothesized to be <2 letters. The sample size was determined considering a two-sided 95% confidence interval (CI) of four letters (precision ± 2 letters) for an estimated standard deviation (SD) of 7.5 letters in each group, and a sample size of 220 patients (110 patients in each group) was sufficient to fulfil the primary objective. However, to meet the requirement of the China National Medical Products Administration for safety evaluation of ≥300 patients exposed to ranibizumab, a sample size of 310 patients (155 patients per treatment regimen) was planned to be randomized, assuming that up to five patients per regimen would not receive any ranibizumab injection. Assuming that 10% of the 300 treated patients would not contribute to the primary outcome in this study, a sample size of 270 patients (135 per treatment regimen) would produce a 95% CI of ±1.8 letters from the mean average BCVA change to the limits when the estimated SD was 7.5 letters for each regimen. Thus, the study was overpowered for the analysis of the primary end-point.

Statistical method

Efficacy analyses were performed using the full analysis set (FAS) that included all randomized patients to whom the study treatment was assigned. The primary efficacy outcome was analysed using descriptive statistics, and the 95% CI was assessed. The 95% CIs were derived from the analysis of variance (ANOVA) model with the factors of 'treatment', 'baseline BCVA' (≤50 letters, 51–73 letters, and >73 letters) and 'lesion type' (PCV and non-PCV). The missing values of BCVA from months 4 to 12 were imputed using the FAS based on mean value interpolation and last observation carried forward.

A sensitivity analysis of the primary efficacy variable was performed within the FAS in which only the observed values were used without missing data imputation. A *post hoc* non-inferiority testing between the two arms with a non-inferiority margin of a 5-letter difference in BCVA was also performed.

Secondary and explorative outcomes were analysed descriptively using the FAS, similar to the primary outcome.

Safety was assessed using the safety set, which included all patients who received at least one injection of ranibizumab and had at least one postbaseline safety assessment, including patients who reported no AEs.

Results

Patient disposition and baseline characteristics

Of the 334 randomized patients, 313 (94%) completed 12 months and 283 (85%) completed 24 months (Fig. 1). A total of 333 patients were included in the FAS (monthly, n = 167; PRN, n = 166); 332 patients (monthly n = 166, PRN n = 166) were included in the safety set.

Baseline demographics and ocular characteristics were similar between the monthly and PRN treatment groups (Table 1). At baseline, all patients

Table 1. Patient baseline demographics and ocular characteristics (FAS).

Characteristics	Ranibizumab 0.5 mg monthly N = 167	Ranibizumab 0.5 mg PRN N = 166	Total N = 333
Age Mean (SD), years	65.6 (8.43)	66.8 (8.31)	66.2 (8.38)
Sex, *n* (%)			
Male	119 (71.3)	119 (71.7)	238 (71.5)
Ethnicity, *n* (%)			
Chinese	167 (100.0)	166 (100.0)	333 (100.0)
Time since first diagnosis of nAMD			
Mean (SD), months	2.8 (8.12)	3.4 (7.39)	3.1 (7.76)
Age at first diagnosis of nAMD			
Mean (SD), years	65.5 (8.44)	66.6 (8.33)	66.0 (8.39)
VA Mean (SD), EDTRS letters	53.5 (13.58)	53.7 (13.36)	53.6 (13.45)
CSFT*, Mean (SD), μm	468.8 (178.18)	488.5 (195.98)	478.7 (187.32)
PCV status*, *n* (%)			
Present	70 (41.9)	69 (41.6)	139 (41.7)
CNV location, *n* (%)			
Subfoveal	68 (97.1)	65 (94.2)	–
Juxtafoveal	1 (1.4)	1 (1.4)	–
Extrafoveal	0 (0.0)	1 (1.4)	–
Could not grade	1 (1.4)	2 (2.9)	–
CNV status, *n* (%)†			
Present	167 (100)	162 (97.6)	329 (98.8)
Type of CNV			
Predominantly classic	30 (18.0)	29 (17.5)	59 (17.7)
Minimally classic	15 (9.0)	13 (7.8)	28 (8.4)
Occult with no classic component	109 (65.3)	111 (66.9)	220 (66.1)
Could not grade	13 (7.8)	10 (6.0)	23 (6.9)
Others	0	3 (1.8)	3 (0.9)
Could not grade	0	4 (2.4)	4 (1.2)

Percentages are based on the total number of patients in the full analysis set.
Ranibizumab 0.5 mg monthly group refers to ranibizumab monthly injection prior to Month 12 followed by PRN.
The FAS included all randomized patients to whom study treatment was assigned.
CFP = colour fundus photography, CNV = choroidal neovascularization, CRC = central reading centre, CSFT = central subfield thickness, FA = fluorescein angiography, FAS = full anaysis set, N = total number of patients, n = number of patients, nAMD = neovascular age-related macular degeneration, PCV = polypoidal choroidal vasculopathy, PRN = *pro re nata*, SD = standard deviation, VA = visual acuity.
* Assessed by CRC.
† Assessed by the FA/CFP system.

presented with active CNV secondary to AMD, and 139 (41.7%) patients were diagnosed with PCV lesions. Baseline characteristics of patients with and without PCV are given in the Table S1.

Efficacy

Best-corrected visual acuity (BCVA) increased rapidly in both treatment groups, especially during the first 3 months of the study. At Month 3, when patients, regardless of treatment assignment, had received at least three monthly treatments with ranibizumab 0.5 mg, the mean change in BCVA from baseline was +8.0 letters in the monthly group and +7.2 letters in the PRN group. The mean average BCVA increased from Month 3 to Month 4 through Month 12 in both regimens (monthly regimen, 3.3 letters; PRN regimen, 1.7 letters). The least square mean difference in this increase between both regimens was 1.6 letters (95% CI: −2.95, −0.20; Table 2). A *post hoc* non-inferiority testing with a non-inferiority margin of a 5-letter difference in BCVA provided a p value of <0.0001. The mean BCVA with both treatment regimens increased from baseline to Month 12 and was stable during the second year of the study (months 13–24), when all patients received ranibizumab according to a PRN regimen (Fig. 2A and Table S2). The BCVA change was consistent in both subgroups of patients, with and without PCV (Fig. 2B).

The visual outcomes in terms of categorized BCVA change are provided in Fig. S1. The number of patients who gained ≥15 letters in BCVA was slightly higher with the ranibizumab 0.5 mg monthly regimen than with the PRN regimen, while the number of patients with a loss of <15 letters or gain of ≥30 letters was comparable between both treatment regimens (Fig. S1). Although the proportion of patients who had a BCVA score of ≥73 letters was higher with the monthly regimen at Month 12 than with the PRN regimen (41.2% versus 33.7%), it was similar at Month 24 (38.2% versus 35.5%). Categorized gain and loss in BCVA by PCV baseline status are presented in Figs S2 and S3, respectively. The proportion of patients with BCVA ≥69 ETDRS letters were comparable between PCV and non-PCV subgroups at months 12 and 24 (Fig. S4).

Table 2. Mean average BCVA change (ETDRS letters) from Month 3 to Month 4 through Month 12 in the treatment regimens (FAS).

Parameter		Ranibizumab 0.5 mg monthly *N* = 167	Ranibizumab 0.5 mg PRN *N* = 166
Month 3	*n*	162	159
	Mean (SD)	62.2 (14.52)	61.4 (15.36)
	SE	1.14	1.22
	Median	64.0	64.0
Average BCVA change from Month 3 to Month 4 through Month 12	*n*	162	159
	Mean (SD)	3.3 (5.61)	1.7 (6.87)
	SE	0.44	0.55
	Median	2.5	1.1
Comparison of PRN versus monthly	Difference in LS means*	–	−1.6
	95% CI for difference*	–	(−2.95, −0.20)

Two-sided 95% CIs are based on t-distribution for individual means and differences in means
The FAS included all randomized patients to whom study treatment was assigned.
ANOVA = analysis of variance, BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS = full analysis set, LS = least square, *N* = total number of patients, *n* = number of patients with a value for both Month 3 and average of Month 4 to Month 12, PRN = *pro re nata,* SD = standard deviation, SE = standard error.
* Differences in LS means and their two-sided 95% CIs were estimated from the ANOVA model with factors treatment, baseline BCVA (<51 letters, 51–73 letters, and >73 letters).

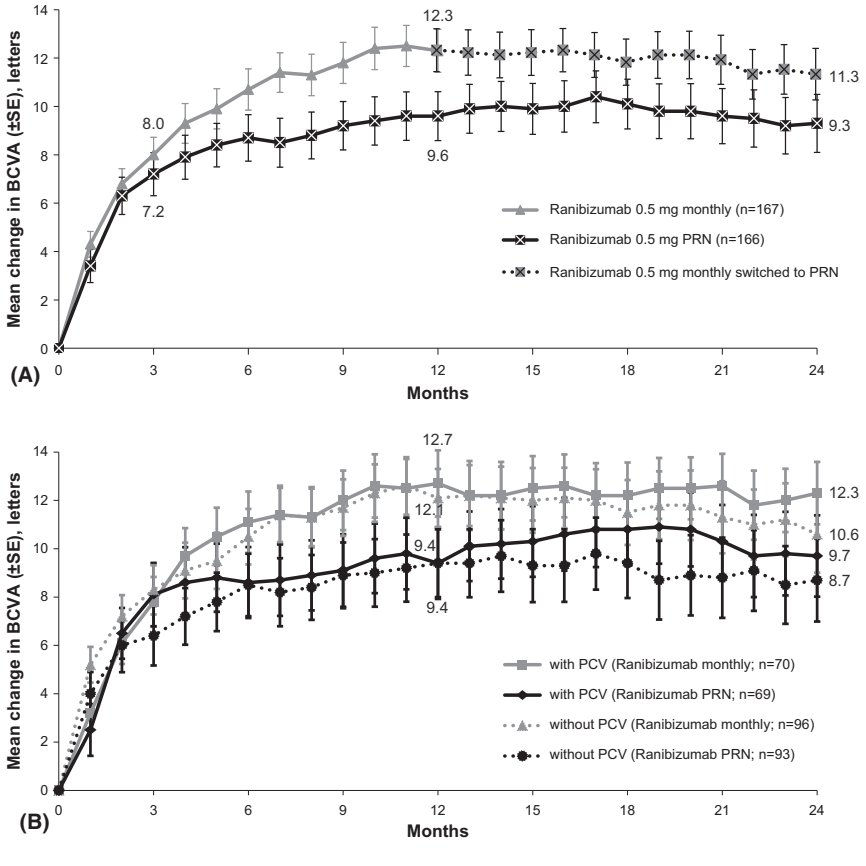


Fig. 2. Mean change in BCVA (ETDRS letters) in the study eye from baseline over time (FAS): (A) overall population; (B) subgroups of patients with and without PCV. The ranibizumab monthly group received ranibizumab monthly injections prior to Month 12, and PRN thereafter. The FAS included all randomized patients to whom study treatment was assigned. BCVA = best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS = full analysis set, *n* = number of patients with a value for both baseline and respective time-points PCV = polypoidal choroidal vasculopathy, PRN = *pro re nata*, SE = standard error.

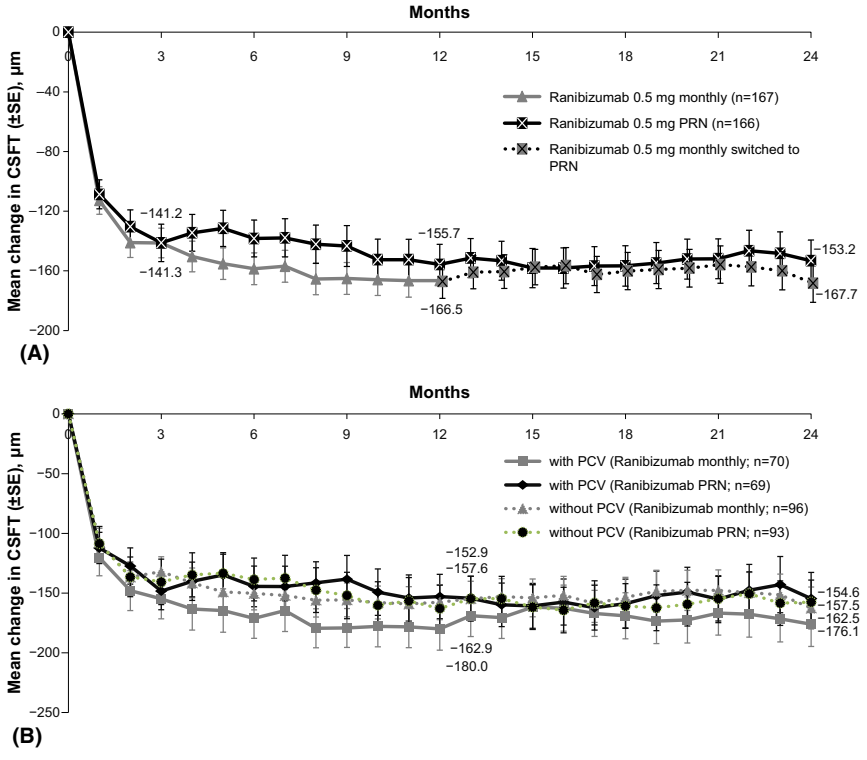


Fig. 3. Mean change in CSFT (μm) in the study eye from baseline over time (FAS): (A) overall population; (B) subgroups of patients with and without PCV. The ranibizumab monthly group received ranibizumab monthly injections prior to Month 12 and PRN thereafter. The FAS included all randomized patients to whom study treatment was assigned. CSFT = central subfield thickness, FAS = full analysis set, *n* = number of patients with a value for both baseline and respective time-points, PCV = polypoidal choroidal vasculopathy, PRN = *pro re nata*, SE = standard error.

A decrease in mean CSFT was observed early (mainly during the first 2 months) with both treatment regimens and was maintained thereafter until the end of the study (Fig. 3A). A similar trend was observed in patients with and without PCV (Fig. 3B).

Treatment exposure

The mean number of ranibizumab injections from Day 1 to Month 11 was 11.4 with the monthly regimen versus 8.2 with the PRN regimen. From Month 12 to Month 23 when both arms received PRN treatment, all patients received a similar mean number of ranibizumab injections: 4.8 and 5.1 injections in the monthly and PRN regimens, respectively (Table 3). Mean number of injections was similar for patients with and without PCV (Day 1–Month 11: monthly, 11.2 versus 11.5; PRN, 8.4 versus 8.2 and Month 12–23: monthly, 4.9 versus 4.7; PRN, 6.0 versus 4.5).

The duration of the ranibizumab treatment-free interval in the study eye was defined as the number of visits (whether attended or not) where ranibizumab was not administered. In the ranibizumab monthly group, treatment-free intervals were only possible during the second year of the study with PRN treatment regimen. The mean duration of the first, second and third treatment-free interval prior to Month 12, for the ranibizumab PRN group, was 2.7, 2.0 and 1.3 months, respectively. Prior to Month 24, the mean duration of ranibizumab treatment-free intervals was longer in the ranibizumab PRN group than in the ranibizumab monthly group for the first (3.7 months versus 2.9 months), second (3.3 months versus 2.1 months) and third (3.0 months versus 1.5 months) ranibizumab treatment-free interval.

Safety

One death was reported in the PRN regimen group following a myocardial infarction SAE that was not suspected by the investigator to be related to treatment with ranibizumab and/or ocular injection.

Serious AEs (SAEs) were reported in 14.5% of patients in each of the treatment groups. The rate of ocular SAEs was 1.2% for each treatment regimen (Table 4); these were considered treatment related in 0.6% of patients (monthly) and 1.2% of patients (PRN) and related to ocular injections in 0.6% of patients in each treatment group. Non-ocular SAEs were reported in 12.7% (monthly) and 13.3% (PRN) of patients (Table 4).

Ocular AEs were reported in 32.5% (monthly) and 27.1% (PRN) of patients, with conjunctival haemorrhage as the most frequent AE (12.7% in monthly and 6.6% in PRN, Table 4). Ocular AEs were considered treatment related in 3.0% of monthly patients and 4.2% of patients in the PRN regimen; 15.4% of these AEs were attributed to ocular injections.

Discussion

DRAGON was the first clinical study to investigate the efficacy and safety of a ranibizumab PRN treatment regimen in Chinese patients with nAMD with presence or absence of PCV at baseline for a 2-year duration. This study demonstrated that both ranibizumab 0.5 mg monthly and PRN regimens were effective in improving vision in Chinese patients with nAMD. Patients achieved notable BCVA gains of 12.3 and 9.6 letters with 11.4 and 8.2 injections up to Month 12 with monthly and PRN regimens, respectively. Best-corrected visual acuity (BCVA) gains and CSFT reductions observed in the first year were maintained during the second year with approximately five injections, when all patients received ranibizumab according to a PRN regimen. The results in subgroups of patients with or without PCV were comparable to the overall population.

The difference of 1.6 letters in mean average BCVA score between the two regimens from Month 4 to Month 12 compared with Month 3 was relatively small (95% CI: −2.95, −0.20; *post hoc* $p < 0.0001$ with a non-inferiority margin of five letters). Due to the sample size, the study was overpowered for this analysis, and therefore, testing provided with a p value is not very meaningful. No new safety signals were reported.

Table 3. Number of ranibizumab injections by time period (safety set).

Time period	Ranibizumab 0.5 mg monthly *N* = 166	Ranibizumab 0.5 mg PRN *N* = 166
Day 1 to Month 11		
Number of injections		
Mean (SD)	11.4 (1.90)	8.2 (2.65)
Median	12	8
Frequency of injections—*n* (%)		
1	1 (0.6)	0
2	1 (0.6)	1 (0.6)
3	2 (1.2)	9 (5.4)
4	0	6 (3.6)
5	2 (1.2)	15 (9.0)
6	2 (1.2)	13 (7.8)
7	2 (1.2)	17 (10.2)
8	2 (1.2)	27 (16.3)
9	0	16 (9.6)
10	2 (1.2)	22 (13.3)
11	18 (10.8)	20 (12.0)
12	134 (80.7)	20 (12.0)
Months 12–23		
Mean (SD)	4.8 (3.81)	5.1 (3.84)
Median	4.0	5.0
Day 1 to Month 23		
Mean (SD)	15.8 (4.77)	12.9 (5.89)
Median	15	12

Both treatment regimens included PRN treatment from Month 12 to 24.
The ranibizumab 0.5 mg monthly regimen refers to a ranibizumab monthly injection prior to Month 12, followed by PRN.
Percentages are based on the total number of patients (*n*) who had not discontinued treatment at start of the specific time period.
The safety set included all patients who had received at least one injection of ranibizumab and had at least one postbaseline safety assessment.
N = total number of patients, *n* = number of patients, PRN = *pro re nata*, SD = standard deviation.

In DRAGON, the average age and proportion of male patients at baseline were similar to those in the EXTEND II study, also conducted in Chinese patients, but differed from other nAMD studies in Caucasians. The mean age of patients in DRAGON and EXTEND II was lower (66.2 and 66.8 years, respectively) than that of Caucasian patients included in the HARBOR (79 years) and CATT (ranibizumab groups, 78.3–79.5 years) studies (CATT Research Group et al. 2012; Busbee et al. 2013; Zhao et al. 2014). The proportion of male patients in DRAGON (71.5%) and EXTEND II (66.7%) was also higher than that in the HARBOR (41%) and CATT studies (ranibizumab groups, 37.6%–40.6%) (CATT Research Group et al. 2012; Busbee et al. 2013; Zhao et al. 2014). These differences may be due to the higher proportion of PCV patients (41.7%) in the DRAGON study. The prevalence of PCV is higher in Asians than in Caucasians, is primarily reported in males, and the younger population (Maruko et al. 2007; Imamura et al. 2010).

Twelve-month BCVA outcomes with a monthly regimen in the DRAGON study were comparable to the results in other studies with Asian patients (e.g. EXTEND II and EXTEND III studies) (Kwon et al. 2012; Zhao et al. 2014). The 12-month open-label EXTEND II study in Chinese patients and the EXTEND III study in South Korean and Taiwanese patients with nAMD showed a BCVA gain of 12.7 letters and 10.1 letters, respectively, with a monthly regimen and a similar number of ranibizumab injections (mean, 11.5 injections each) (Kwon et al. 2012; Zhao et al. 2014).

The HARBOR study investigated a PRN versus monthly treatment with ranibizumab in Caucasian patients with nAMD over 24 months (Ho et al. 2014). The ranibizumab 0.5 mg monthly and PRN regimens led to a mean change in BCVA of +10.1 letters and +8.2 letters, respectively, at Month 12 with a corresponding mean number of injections of 11.3 and 7.7, respectively (Ho et al. 2014). In the DRAGON study, gains in BCVA were slightly higher than the HARBOR study at Month 12 with a similar mean number of injections. This could be attributed to differences between the study populations. In addition, comparatively younger patients were included in the DRAGON study, which might have led to better visual outcomes, as some studies have shown a correlation between age and visual prognosis (Kaiser et al. 2007; Yamashiro et al. 2012). It is also reported that early diagnosis and treatment of nAMD may be associated with a better visual outcome (Matthe & Sandner 2011; Schwartz & Loewenstein 2015). Nevertheless, these data should be compared with caution with other studies due to other differences, such as study design, study duration, patient population and treatment regimens. The overall results of the DRAGON study at Month 12 are also in line with the findings of the EXTEND I study in Asians, in which the ranibizumab PRN regimen resulted in similar and sustainable BCVA improvements with less frequent injections in comparison with the monthly regimen (Tano et al. 2011). In DRAGON study, mean duration of ranibizumab treatment-free intervals was longer in the PRN group than in the monthly group, which is expected as for the PRN group there was a longer period when treatment did not have to be administered monthly.

The above results from clinical studies suggest that a PRN regimen may be considered for better patient compliance and may decrease healthcare burden (Tano et al. 2011; Ho et al. 2014). However, data from uncontrolled retrospective analyses have shown that a PRN regimen that resulted in fewer than five injections in the first year along with irregular follow-up was insufficient to achieve and sustain VA improvements (Cohen et al. 2009; Dadgostar et al. 2009; Wolf & Kampik 2014). Some studies have shown that a PRN regimen may not lead to improvement of VA due to a reduced number of retreatments, but may sustain VA gains achieved with initial monthly treatment (Holz et al. 2011). In the DRAGON study, patients in both treatment arms were required to

Table 4. Incidence of adverse events over 24 months (safety set).

Preferred term *n* (%)	Ranibizumab 0.5 mg monthly *N* = 166	Ranibizumab 0.5 mg PRN *N* = 166
Death	0	1 (0.6)
Non-ocular SAEs*	21 (12.7)	22 (13.3)
Cerebral infarction	4 (2.4)[†]	1 (0.6)
Angina pectoris	2 (1.2)	0
Coronary artery disease	2 (1.2)	1 (0.6)
Lacunar infarction	0	2 (1.2)
Ocular SAEs (study eye)	2 (1.2)	2 (1.2)
Cataract traumatic	1 (0.6)	0
Retinal detachment	1 (0.6)	0
Vitreous haemorrhage	0	2 (1.2)
Non-ocular AEs[‡]	98 (59.0)	82 (49.4)
Nasopharyngitis	24 (14.5)	18 (10.8)
Upper respiratory tract infection	14 (8.4)	7 (4.2)
Blood glucose increased	10 (6.0)	5 (3.0)
Cough	8 (4.8)	7 (4.2)
Hypertension	8 (4.8)	9 (5.4)
Dizziness	5 (3.0)	7 (4.2)
Blood uric acid increased	4 (2.4)	5 (3.0)
Ocular AEs[§]	54 (32.5)	45 (27.1)
Conjunctival haemorrhage	21 (12.7)	11 (6.6)
Conjunctivitis	5 (3.0)	2 (1.2)
Visual acuity reduced	5 (3.0)	1 (0.6)
Eye pain	4 (2.4)	1 (0.6)
Foreign body sensation	4 (2.4)	2 (1.2)
Intraocular pressure increased	4 (2.4)	12 (7.2)
Lacrimation increased	4 (2.4)	1 (0.6)
Retinal haemorrhage	3 (1.8)	5 (3.0)

A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category.
The ranibizumab 0.5 mg monthly group refers to a ranibizumab monthly injection prior to Month 12, followed by PRN.
The safety set included all patients who had received at least one injection of ranibizumab and had at least one postbaseline safety assessment.
AE = adverse event, SAE = serious adverse event, *N* = total number of patients, *n* = number of the patients with at least one AE in the corresponding category; PRN = *pro re nata*
* SAE reported in> 1% of patients receiving either regimen is shown here.
[†] One of the SAEs occurred within 30 days after end of the study.
[‡] ≥3% patients in either group.
[§] ≥2% patients in either group.

return for monthly visits. It was recognized that the monitoring of patients in clinical practice may differ, including longer intervals than monthly visits in patients receiving ranibizumab in a PRN regimen. However, regulated monthly monitoring visits, diagnostic evaluations and strict retreatment criteria are considered essential for favourable visual outcomes with a PRN regimen.

Clinical studies have evaluated the efficacy of ranibizumab treatment in patients with PCV (Koh et al. 2012; Oishi et al. 2013; Koh et al. 2017). In the EVEREST II study, BCVA gains with ranibizumab treatment at Month 12 were lower, with fewer injections compared with the DRAGON study (Koh et al. 2017). This difference may be attributed to variations in the baseline VA, study design, patient demographics, enrolment criteria and treatment regimens in the two studies. The LAPTOP study also demonstrated that ranibizumab, given as three consecutive monthly injections followed by a PRN regimen, was efficacious in terms of VA gain in patients with PCV at 12 months (change of VA [logarithm of the minimum angle of resolution]: 0.49 to 0.38 ($p = 0.003$)] (Oishi et al. 2013).

The 12-month VA gains with ranibizumab in PCV patients from DRAGON study were similar to that with aflibercept (10.7 letters) in PLANET study (Lee et al. 2018). ALTAIR and HAWK (Ogura et al. 2019) studies have also demonstrated the efficacy of anti-VEGF drugs, aflibercept and brolucizumab, respectively, in Japanese nAMD patients with PCV (Ohji et al. 2020). In contrast, some studies in Caucasian patients have suggested increased anti-VEGF resistance or poor response to ranibizumab in PCV patients with presumed nAMD, thus requiring additional treatment (Stangos et al. 2010; Hatz & Prunte 2014).

In this study, CSFT reduction with ranibizumab from baseline up to Month 12 in patients with PCV was greater than that reported with ranibizumab monotherapy (−113.4 μm) in the 12-month EVEREST II study (Koh et al. 2017). The PLANET study results showed similar CSFT reduction (−137.7 μm) at Month 12 with aflibercept in this population (Lee et al. 2018).

No new safety concerns were identified in this study. One patient died due to myocardial infarction; however, this was not suspected by the investigator to be related to ranibizumab and/or the ocular injection. The rates of ocular SAEs were low (1.2% for both monthly and PRN groups) compared with studies in Caucasian patients (e.g. HARBOR, ranibizumab 0.5 mg groups; monthly, 2.6%; PRN, 2.5%) with no cases of endophthalmitis (Ho et al. 2014).

Due to the resemblance of PCV to other forms of AMD [classic CNV and central serous chorioretinopathy (CSC)], the diagnosis of PCV and distinguishing it from other retinal conditions can be challenging and may potentially lead to inappropriate treatment (Wong et al. 2016). For example, the efficacy of anti-VEGF therapy in treating CSC is not established. Thus, in clinical practice, accurate diagnosis of PCV is essential for optimal treatment of such patients.

One of the key strengths of the DRAGON study were involvement of a CRC for an accurate diagnosis of PCV at baseline by use of ICGA. Other strengths included involvement of both monthly and PRN regimens for evaluating the benefits of ranibizumab in patients with nAMD, irrespective of presence or absence of baseline PCV. Moreover, results of the DRAGON study add to the existing evidence on ranibizumab treatment in patients with nAMD and PCV and should be taken into consideration when providing

guidance on treatment of such patients. This study included only Chinese patients; nevertheless, to our knowledge, no evidence has suggested differential ethnic responses in nAMD or PCV. The study was limited by the investigator-driven PRN treatment decision with no involvement of the CRC. Another limitation was the use of a PRN regimen in the second year in both monthly and PRN groups; this only allowed comparison of the two regimens up to Year 1.

In conclusion, ranibizumab administered, either as monthly in Year 1 followed by PRN in Year 2 or monthly loading doses followed by PRN regimen up to Year 2, resulted in VA improvement in Chinese patients with nAMD, irrespective of PCV status at baseline. The safety data were consistent with the well-established safety profile of ranibizumab, and no unexpected drug-related AEs were reported. Although formal statistical testing comparing the two treatment groups was not performed in accordance with a statistical plan, the results of this study demonstrate that initial monthly doses of ranibizumab followed by a PRN regimen with regular follow-ups is an effective and viable approach for treatment of patients with nAMD and PCV.

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Supporting Information

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

Fig. S1. Categorized BCVA change (ETDRS letters) from baseline to Months 3, 12, and 24 (FAS) in the overall population
Fig. S2. Categorized BCVA gains at Months 12 and 24 in patients with PCV and without PCV (FAS)
Fig. S3. Proportion of patients with BCVA loss from baseline at Months 12 and 24 in with and without PCV subgroups (FAS).
Fig. S4. Proportion of patients with BCVA ≥69 ETDRS letters at baseline and at Months 12 and 24 in with and without PCV subgroups (FAS).
Fig. S5. Proportion of patients with dry retina at baseline and Months 12 and 24 in with PCV and without PCV subgroups (FAS).
Table S1. Demographics and baseline ocular characteristics in patients with and without PCV (FAS).
Table S2. BCVA (letters) at baseline and Months 3, 12 and 24 (FAS).