Ophthalmol Ther (2024) 13:935–954
https://doi.org/10.1007/s40123-024-00888-0

ORIGINAL RESEARCH

Six-Year Outcomes in Subjects with Polypoidal Choroidal Vasculopathy in the EVEREST II Study

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Received: November 20, 2023 / Accepted: January 11, 2024 / Published online: February 3, 2024

ABSTRACT

Introduction: The EVEREST II study previously reported that intravitreally administered ranibizumab (IVR) combined with photodynamic therapy (PDT) achieved superior visual gain and polypoidal lesion closure compared to IVR alone in patients with polypoidal choroidal vasculopathy (PCV). This follow-up study reports the long-term outcomes 6 years after initiation of the EVEREST II study.

Methods: This is a non-interventional cohort study of 90 patients with PCV from 16 international trial sites who originally completed the EVEREST II study. The long-term outcomes were assessed during a recall visit at about 6 years from commencement of EVEREST II.

Results: The monotherapy and combination groups contained 41 and 49 participants, respectively. The change in best-corrected visual acuity (BCVA) from baseline to year 6 was not different between the monotherapy and combination groups; − 7.4 ± 23.0 versus − 6.1 ± 22.4 letters, respectively. The combina-

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tion group had greater central subfield thickness (CST) reduction compared to the monotherapy group at year 6 (− 179.9 vs − 74.2 µm, $p = 0.011$). Fewer eyes had subretinal fluid (SRF)/intraretinal fluid (IRF) in the combination versus monotherapy group at year 6 (35.4% vs 57.5%, $p = 0.032$). Factors associated with BCVA at year 6 include BCVA (year 2), CST (year 2), presence of SRF/IRF at year 2, and number of anti-VEGF treatments (years 2–6). Factors associated with presence of SRF/IRF at year 6 include combination arm (OR 0.45, $p = 0.033$), BCVA (year 2) (OR 1.53, $p = 0.046$), and presence of SRF/IRF (year 2) (OR 2.59, $p = 0.042$).

Conclusion: At 6 years following the EVEREST II study, one-third of participants still maintained good vision. As most participants continued to require treatment after exiting the initial trial, ongoing monitoring and re-treatment regardless of polypoidal lesion status are necessary in PCV.

Trial Registration: ClinicalTrials.gov identifier, NCT01846273.

Keywords: Polypoidal choroidal vasculopathy; Long-term outcomes; EVEREST II; Anti-vascular endothelial growth factor (VEGF) therapies; BCVA

Key Summary Points

Why carry out this study?

The long-term outcomes of polypoidal choroidal vasculopathy (PCV) are not known, especially the effects of early combination therapy of intravitreal anti-vascular endothelial growth factors and photodynamic therapy.

The aim of this study was to assess the long-term outcome of patients with PCV who completed the EVEREST II study.

What was learned from the study?

In patients who completed the EVEREST II study, there was a decline in final visual acuity which was not significant between groups but anatomical outcomes were better in the combination therapy arm.

Good disease control at the point of study exit and more frequent treatments after study exit were associated with good visual and anatomical outcomes at year 6.

Good outcomes can be achieved in the long term if continued monitoring and re-treatment of PCV is maintained.

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INTRODUCTION

The efficacy of anti-vascular endothelial growth factor (VEGF) therapies has been well established in clinical trials. However, maintaining long-term vision in eyes with age-related macular degeneration (AMD) remains a challenge. The SEVEN-UP study reported that at 7 years after enrolling into the MARINA and ANCHOR trials, patients lost a mean of 8.6 letters [1]. In contrast, a real-world AMD registry study showed a gain of 5.3 letters over 2 years on a treat and extend protocol [2]. The difference in outcomes could be due to sub-optimal versus proactive treatment. In addition, over a longer follow-up, recurrence and development of scarring or atrophy can occur. Polypoidal choroidal vasculopathy (PCV) is a variant of neovascular AMD, characterized by aneurysmal dilatations at the end of a type 1 neovascularization [3–5]. While randomized controlled trials have reported visual improvement up to 2 years [6–9], there is a paucity of long-term outcome data [10, 11]. The EVEREST II study compared the efficacy and safety of intravitreally administered ranibizumab (IVR) alone or in combination with photodynamic therapy (PDT) over a 2-year period. The 2-year results demonstrated that combination was superior to monotherapy in best-corrected visual acuity (BCVA) gain and achieving closure of polypoidal lesions (PLs), with fewer IVR treatments [6]. In addition, an international real-world study comparing the use of combination therapy versus monotherapy to treat PCV showed quicker disease inactivation with combination treatment [12]. However, it remains unclear whether the benefits of initial combination persist beyond year 2, and whether PL closure early on can confer long-term benefits [13, 14]. Recurrence has been found to be one of the main reasons for poor long-term outcome with recurrence rates of 40–78.6% after 3 years of follow-up [14]. However the risk factors for recurrence remain poorly understood. A key unanswered question from the 2-year EVEREST II study is whether the functional and anatomical benefits following combination therapy continue in the long term [15, 16].

The current study aims to report the long-term outcomes, recurrence rates, and treatment needs in eyes with PCV 6 years after first initiation of treatment. A secondary aim is to evaluate whether PL perfusion status at year 2 influences any of the outcome parameters.

METHODS

Study Design

This is a multicenter, cross-sectional study of the long-term outcomes of a cohort of patients originally treated with ranibizumab alone (monotherapy group) or in combination with PDT (combination group) in the EVEREST II study (ClinicalTrials.gov identifier, NCT 01846273). The study was conducted in accordance with the tenets of the Declaration of Helsinki and with approval of respective institutional review boards of the participating centers. This study is investigator-led and funded as part of a grant on Asian AMD from the Ministry of Health of Singapore through a submission by the Singapore Eye Research Institute. Assistance was provided by Novartis, who compiled the database of completers, which included information on the randomization arm, BCVA, and anatomical outcomes at the exit visit of EVEREST II at year 2.

Study Cohort

A total of 332 participants were enrolled in the original EVEREST II study and 274 completed the month 24 visit. For the purpose of this follow-up study, only sites with a minimum of five completers were invited (21/32 sites with 230/274 potential participants) to limit administrative burden. Sixteen sites with a potential of 176 participants participated in the follow-up study and contributed data on a total of 92 participants. All participating patients provided informed consent for the 6-year follow-up examination and for their investigators to access medical records of any additional assessments/treatments they had received after exiting from the original EVEREST II study.

Examination Procedures

Participants were evaluated during a single study visit which takes place 6 years (± 6 months) after enrolment to the original EVEREST II study. Patients were interviewed about treatment to either eye, visits to ophthalmologists, or serious medical events since their exit visit of the EVEREST II study. Examination procedures during this visit include BCVA measurement recorded as logarithm of the minimum angle of resolution (logMAR) letters, a dilated eye examination, spectral domain optical coherence tomography (OCT), fundus color photography, fluorescein angiography (FA), and indocyanine green angiography (ICGA). Chart review of the period between exiting EVEREST II and the follow-up visit was performed for evidence of re-treatment by the interval physician. Where available, the number of interval treatments with anti-VEGF agents (ranibizumab, bevacizumab, or aflibercept) or other PCV treatments (PDT, thermal laser) were recorded.

Outcome Measures

The primary aim of the study was to report the long-term BCVA changes from baseline to year 2 (exit of the EVEREST II study) and to year 6. This includes the mean BCVA change in logMAR letters and proportion of eyes with good vision ($\geq$ 69 letters) and poor vision ($<$ 36 letters). Secondary anatomical outcomes included central retinal thickness (CRT), presence of intraretinal fluid (IRF) or subretinal fluid (SRF), presence of pigment epithelial detachment (PED), presence of PL, presence of geographic atrophy, and presence of fibrosis from baseline to year 2 and to year 6.

Statistical Analysis

Anonymized data were collected on case report forms and sent to the Singapore Eye Research Institute where data were entered manually into an encrypted online database (REDCap Software, 8.1.12). De-identified data were exported for statistical analysis.

Descriptive data included the mean (standard deviation [SD]), median (1st and 3rd quartile [Q1, Q3]) and percentages where appropriate. Statistical tests such as Student's *t* test, Wilcoxon rank sum, and Fisher's tests were used where appropriate to compare baseline and year 2 characteristics between the monotherapy and combination groups. To account for potential effects of different healthcare-funding models, outcomes were analyzed by dividing the cohort into countries that received reimbursement for AMD treatment (Japan, Korea, Taiwan) and countries that received partial or no reimbursement for AMD treatment (Singapore, Malaysia, Hong Kong, Thailand).

The outcomes between (1) treatment groups at 6 years and (2) reimbursement groups were assessed by a mixed effects longitudinal generalized additive model with the therapy group and time as the main predictor variable adjusted for fixed effects (age, baseline vision, CST, and PL status), and site as the random effect. The numbers of treatments (injections, PDT, and focal lasers) were compared by a Poisson regression model adjusted for age, baseline VA, baseline CST, and time of follow-up as an offset variable. Locally weighted scatterplot smoothing (LOESS) curves were used to analyze change in BCVA throughout the follow-up for different analysis. A p value of less than 0.05 was considered statistically significant. All analyses were conducted using R version 4.0.0.

RESULTS

Study Population and Characteristics at 6-Year Examination

A total of 90 of 176 eligible participants eventually consented to and attended the follow-up examination. Participants were from Japan (n = 20), Korea (n = 19), Singapore (n = 14), Hong Kong (n = 14), Malaysia (n = 10), Taiwan (n = 7), and Thailand (n = 6) (Fig. 1) The most common reason for non-enrolment was loss to follow-up and inability to contact participant.

The characteristics of the participants who provided data to the 6-year follow-up

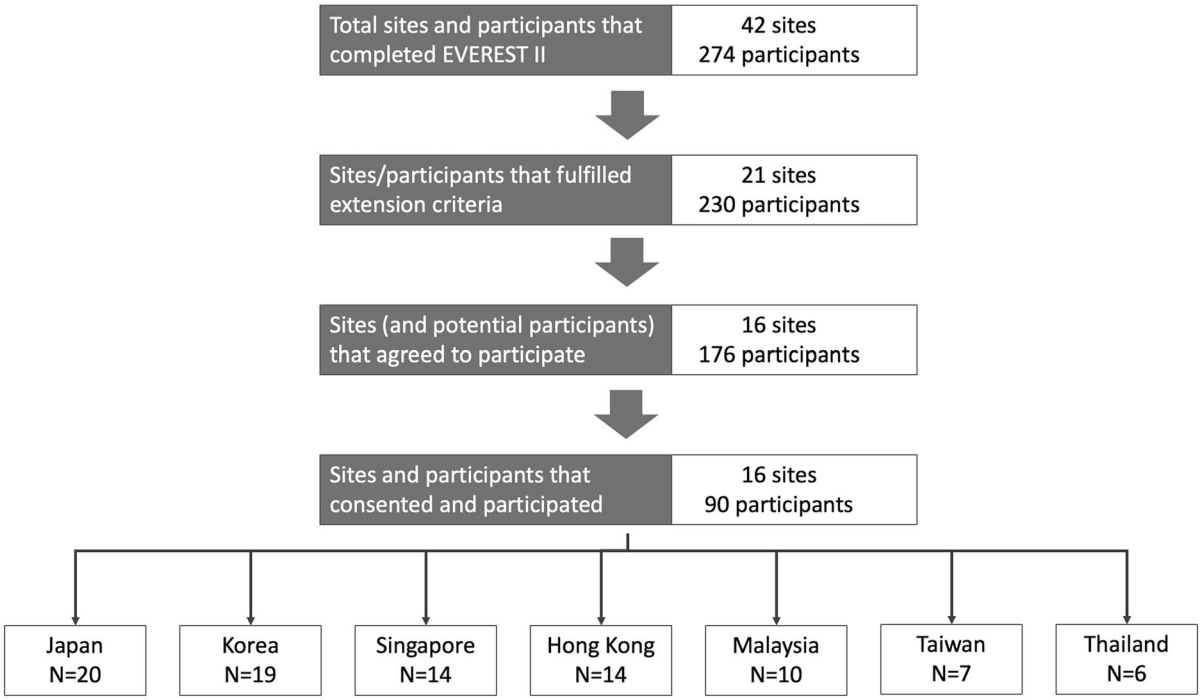


Fig. 1 Participants and sites in EVEREST II extension study. Distribution of participants across sites and from initial EVEREST II trial to the extension study

examination are summarized in Table 1. Forty-one participants (45.5%) were in the monotherapy arm and 49 participants (54.5%) were in the combination arm during the original study. Compared to the overall EVEREST II completers, participants had better BCVA at baseline (monotherapy group 65.6 letters vs 61.2 letter; combination group 63.0 letters vs 61.1 letters) and had experienced a smaller gain in vision at 2 years from baseline (monotherapy group + 2.3 vs + 5.5 letters; combination group + 5.2 vs + 9.6 letters). The mean interval between the baseline visit of EVEREST II study and the follow-up examination was 6.1 ± 0.6 years (range 4.7–7.4 years). New active neovascularization developed in the fellow eye in 5 (monotherapy) and 6 eyes (combination) during the follow-up period.

BCVA Change Baseline Through Year 6

Visual acuity outcomes are summarized in Table 2 and Fig. 2. The BCVA improved in both monotherapy and combination groups at year 2 but dropped to below baseline at year 6. BCVA at baseline, year 2 and year 6 were 65.6, 67.9, and 58.5 letters (monotherapy) and 63.0, 68.2, and 56.8 letters (combination), respectively. Compared to baseline, the mean change in BCVA were + 2.3 ± 10.8 letters (year 2) and − 7.4 ± 23.0 letters (year 6) in the monotherapy group, and + 5.2 ± 10.2 letters (year 2) and − 6.1 ± 22.4 letters (year 6) in the combination group (Fig. 2a). The corresponding median changes in BCVA were + 1.1 letters (IQR − 2.0; + 9.1) (year 2) and − 8.0 letters (IQR − 18.2 to + 6.3) (year 6) in the monotherapy group, and + 4.0 letters (IQR + 1.2; + 12.4) (year 2) and − 8.0 letters (IQR − 19.8; + 4.2) (year 6) in the combination group. The proportion of eyes with BCVA ≥ 69 letter was 45% (monotherapy) and 42.9% (combination) at baseline, which increased to 65% (monotherapy) and 63.3% (combination) at year 2 but reduced to 34.1% (monotherapy) and 29.2%(combination) at year 6. The proportion of eyes with BCVA < 36 letters was 5.0% and 4.1% (baseline), 5.0% and 8.2% (year 2), increasing to 17.1% and 18.8% (year 6) in the monotherapy and combination

Table 1 Comparison of 6-year follow-up participants with all year 2 completers

	Monotherapy		Combination	
	6-year follow-up $N = 41$	Year 2 completers $N = 128$	6-year follow-up $N = 49$	Year 2 completers $N = 146$
Age at exit of EVEREST II, mean (SD)	68.4 (5.4)	68.2 (9.0)	69.7 (6.6)	68.1 (8.5)
Gender, male (%)	33 (80.5)	75.3%	32 (65.3)	64.9%
Baseline characteristics				
BCVA, letters, mean (SD)	65.6 (14.2)	61.2 (13.9)	63.0 (13.6)	61.1 (12.6)
Proportion with ≥ 15 letter gain, %	12.5	24.2	16.3	30.8
Central subfield thickness, μm, mean (SD)	406.7 (119.5)	410.4 (170.9)	457.1 (161.8)	415.9 (143.7)
Characteristics at year 2				
BCVA gain, letters, mean (SD)	2.3 (10.8)	5.5 (1.2)	5.2 (10.2)	9.6 (1.0)
CST reduction in μm, mean (AD)	− 98.9 (128.0)	− 109.3 (142.2)	− 197.2 (175.8)	− 152.9 (129.7)
Proportion with detectable polypoidal lesions, *n* (%)	26 (65.0)	63 (73.3)	13 (26.5)	42 (43.7)

arms, respectively (Fig. 2b). The proportion of eyes with 15 letter gains and loss is summarized in Fig. 2c. None of the comparisons between monotherapy and combination groups was statistically significant.

Change in Anatomical Outcomes from Baseline Through Year 6

Anatomical outcomes are summarized in Table 2 and Fig. 3. CST reduction was seen in both groups at year 2 and remained below baseline at year 6. CST values at baseline, year 2, and year 6 were 406.7, 307.8, and 332.0 μm (monotherapy) and 457.1, 259.9, and 276.5 μm (combination) (Fig. 3a). After we corrected for baseline CST, greater CST reduction was seen in the combination group at year 2 (− 197.2 μm vs − 98.9 μm, $p < 0.01$) and at year 6 (− 179.9 μm vs − 74.2 μm, $p = 0.01$). The proportion of eyes with presence of fluid (SRF and/or IRF) was significantly lower in the combination group at year 2 (40.8% vs 72.5%, $p < 0.01$) and at year 6 (35.4% vs 57.5%, $p = 0.03$). The proportion of eyes with PL detected on ICGA was significantly lower in the combination group (26.5% and 65.0%, $p < 0.01$) at year 2 but at year 6 was not significantly different (45.8% combination vs 55.0% monotherapy, $p = 0.52$) (Fig. 3b). Representative case examples are included in Fig. 4.

Treatment Exposure Between Year 2 and Year 6

Treatment exposure is summarized in Table 3. Between year 2 and year 6, 75.6% (monotherapy) and 75.5% (combination) of eyes received additional treatments. The total number of visits during this 4-year study period was 16.9 ± 9.1 (monotherapy) and 17.2 ± 11.9 (combination). The number of anti-VEGF injections received was lower in the combination arm compared to the monotherapy arm (6.7 ± 2.0 vs 8.6 ± 3.8, $p < 0.01$). Patients in the combination arm received a mean of 2.5 injections between year 2 and 3, 3.4 between year 3 and 4, 2.0 between year 4 and 5, and 2.0 between year 5 and 6, while patients in the monotherapy arm received a mean of 1.6, 2.7, 3.5, and 2.1 injections, respectively. There were fewer PDT treatments (0.4 vs 0.6, $p = 0.07$) and focal laser (0.02 vs 0.12, $p = 0.07$) in the

Table 2 Functional and anatomical outcomes at year 2 and year 6 from baseline

	Monotherapy (*N* = 41)	**Combination (*N* = 49)**	***p*[a]**
BCVA			
Baseline, letters, mean (SD)	65.6 (14.2)	63.0 (13.6)	0.38
Year 2, letters, mean (SD)	67.9 (14.3)	68.2 (14.1)	0.92
Year 6, letters, mean (SD)	58.5 (21.7)	56.8 (20.1)	0.70
BCVA change from baseline			
Year 2, letters, mean (SD)	+ 2.3 (10.8)	+ 5.2 (10.2)	0.20
Year 6, letters, mean (SD)	− 7.4 (23.0)	− 6.1 (22.4)	0.80
Proportion with BCVA ≥ 69 letters			
Baseline, *n* (%)	18 (45.0)	21 (42.9)	0.93
Year 2, *n* (%)	26 (65.0)	31 (63.3)	0.83
Year 6, *n* (%)	14 (34.1)	14 (29.2)	0.88
Proportion with BCVA < 36 letters			
Baseline, *n* (%)	2 (5.0)	2 (4.1)	0.90
Year 2, *n* (%)	2 (5.0)	4 (8.2)	0.84
Year 6, *n* (%)	7 (17.1)	9 (18.8)	0.88
Proportion ≥ 15 letters gain			
Year 2, *n* (%)	5 (12.5)	8 (16.3)	0.84
Year 6, *n* (%)	3 (7.5)	1 (2.1)	0.48
Proportion ≥ 15 letters loss			
Year 2, *n* (%)	2 (5.0)	2 (4.1)	1.0
Year 6, *n* (%)	13 (32.5)	18 (37.5)	0.79
Central subfield thickness, mm			
Baseline, mean (SD)	406.7 (119.5)	457.1 (161.8)	0.11
Year 2, mean (SD)	307.8 (107.2)	259.9 (86.5)	0.02
Year 6, mean (SD)	332.0 (156.5)	276.5 (133.9)	0.08
CST change, mm			
Year 2, mean (SD)	− 98.9 (128.0)	− 197.2 (175.8)	< 0.01
Year 6, mean (SD)	− 74.2 (165.3)	− 179.9 (209.5)	0.01
Presence of both SRF/IRF			
Year 2, *n* (%)	29 (72.5%)	20.0 (40.8%)	< 0.01
Year 6, *n* (%)	23 (57.5%)	17 (35.4%)	0.03
Presence of polypoidal lesions			
Year 2, *n* (%)	26 (65.0)	13 (26.5)	< 0.01

Table 2 continued

	Monotherapy (N = 41)	Combination (N = 49)	p[a]
Year 6, *n* (%)	22 (55.0)	22 (45.8)	0.52
Presence of PED at year 6, *n* (%)	26 (65.0)	28 (59.6)	0.77
Presence of fibrosis at year 6, *n* (%)	4 (9.8)	13 (26.5)	0.08
Presence of atrophy at year 6, *n* (%)	1 (2.4)	5 (10.2)	0.30

[a]The outcomes between treatment groups at 6 years were assessed by a mixed effects longitudinal generalized additive model with the therapy group and time as the main predictor variable adjusted for fixed effects (age, baseline vision, CST, and PL status), and site as the random effect

Table 3 Treatment exposure between year 2 and year 6

	Monotherapy (N = 41)	Combination (N = 49)	p value[a]
Total visits between year 2 and year 6	16.9 (9.1)	17.2 (11.9)	0.89
Any treatment between year 2 and year 6, mean (SD)	31 (75.6)	37 (75.5)	1
Anti-VEGF injection, mean (SD)			
Baseline to year 2, mean (SD)	12.5	8.1	< 0.01
Year 2 to year 6, mean (SD)	8.6 (3.8)	6.7 (2.0)	< 0.01
Active PDT			
Baseline to year 2, mean number of treatments (SD)	Prohibited	2.2	NA
Year 2 to year 6, mean number of treatments (SD)	0.6 (0.9)	0.4 (0.8)	0.07
Number of eyes that received PDT (%)	15 (36.6%)	13 (25.5%)	0.42
Focal laser			
Baseline to year 2, mean number of treatments (SD)	Prohibited	Prohibited	NA
Year 2 to year 6, mean number of treatments (SD)	0.12 (0.05)	0.02 (0.01)	0.07
Number of eyes that received focal laser (%)	3 (7.3%)	1 (4.4%)	0.48

Focal laser: 3 eyes (monotherapy) and 1 eye (combination)
[a]The number of treatments (injections, PDT, and focal lasers) were compared by a Poisson regression model adjusted for age, baseline VA, baseline CST, and time of follow-up as an offset variable
NA not applicable

combination arm compared to the monotherapy arm. Variation in re-treatments between year 2 and year 6 was noted between the seven countries, with the proportion of eyes receiving additional treatments ranging from 42.9% to 100% (p = 0.0231) and the mean number of additional treatments ranging from 2.3 to 10.7 (p = 0.078).

PDT Between Baseline and Year 6

A total of 26 eyes (28.9%) did not receive PDT at any point over the 6 years and were treated with monotherapy only. In this comparison between 26 eyes that never received PDT versus the 64 eyes that received PDT anytime between baseline and year 6, vision at year 6 was similar between eyes that received PDT and those that

Table 4 Factors associated with visual outcome

	Univariate β coefficient (95% confidence intervals)	p	Multivariate β coefficient (95% confidence intervals)	p
Age, year	0.13 (− 0.57 to 0.84)	0.71	0.25 (− 0.38 to 0.87)	0.22
Gender, male	− 3.38 (− 12.75 to 5.99)	0.47	− 1.92 (− 10.32 to 6.47)	0.33
Initial treatment arm, combination	− 1.47 (− 9.97 to 7.04)	0.73	− 4.35 (− 12.25 to 3.54)	0.14
Baseline BCVA, letters	− 4.24 (− 7.17 to − 1.32)	< 0.01	− 1.89 (− 5.61 to 1.83)	0.16
Year 2 BCVA, letters	− 4.09 (− 6.97 to − 1.20)	< 0.01	− 4.90 (− 8.69 to − 1.11)	< 0.01
Baseline CST, 100 µm	− 2.75 (− 5.60 to 0.10)	0.04	− 1.94 (− 4.57 to 0.70)	0.08
Year 2 CST, 100 µm	− 6.92 (− 10.95 to − 2.89)	< 0.01	− 6.94 (− 11.37 to − 2.51)	< 0.01
Total anti-VEGF, year 2–6, *n*	0.54 (0.28 to 0.85)	0.02	0.47 (0.20 to 0.74)	0.03
Total PDT, year 2–6, *n*	− 0.26 (− 0.75 to 0.22)	0.15	− 0.24 (− 0.63 to 0.15)	0.23
Year 2 presence of SRF/IRF	− 12.50 (− 20.60 to − 4.40)	< 0.01	− 12.56 (− 21.07 to − 4.06)	< 0.01
Presence of polypoidal lesions at year 2	0.94 (− 7.59 to 9.47)	0.83	0.42 (− 6.32 to 7.16)	0.85

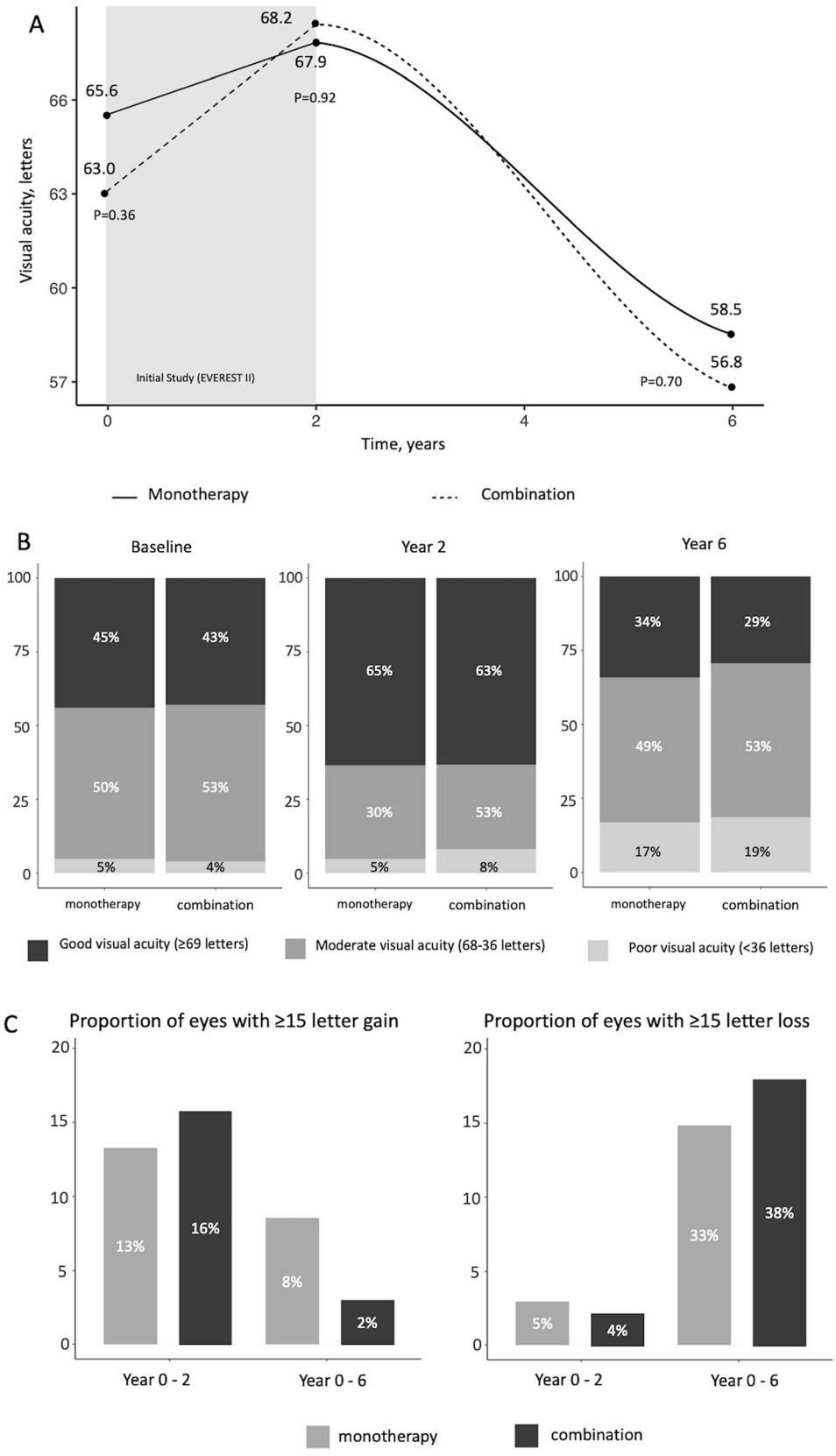
did not (56.0 ± 22.6 versus 58.3 ± 20.0 letters, $p = 0.64$). Final CST, however, was significantly thinner in eyes that received any PDT compared to those that did not (280.4 ± 126.1 µm vs 354.4 ± 179.4 µm, $p = 0.03$). The mean number of injections administered between years 2 and 6 was also significantly lower in eyes that received any PDT compared to those that did not (5.6 ± 6.2 injections vs 10.5 ± 8.7, $p < 0.01$). The proportion of eyes that developed fibrosis (20.3% versus 15.4%, $p = 0.81$) and atrophy (7.8% vs 3.8%, $p = 0.83$) was not statistically significant between eyes that received PDT at any point and eyes that never received PDT.

Additional Analyses

Factors Associated with Outcomes

In the multivariable analysis, factors associated with BCVA at year 6 include BCVA (year 2), CST (year 2), presence SRF/IRF at year 2 and number of anti-VEGF (year 2–year 6) (Table 4). Factors associated with presence of SRF/IRF at year 6 include combination arm (odds ratio [OR] 0.45, 95% CI 0.21–0.99, $p = 0.03$), BCVA (year 2) (OR 1.53, 95% CI 1.01–2.32, $p = 0.04$), and presence of SRF/IRF (year 2) (OR 2.59, 95% CI 0.99–6.74, $p = 0.04$). Regarding the presence of PL at year 6, the only factor showing significant association is PL status (year 2) (OR 3.73, 95% CI 1.55–9.41, $p < 0.01$) (Table 5).

In the comparison between reimbursed and non-reimbursed countries, BCVA improved from baseline to year 2 in both groups during the EVEREST II study but declined to a greater extent in the non-reimbursed group between year 2 and year 6. This pattern was similar after further splitting according to monotherapy and combination. Mean BCVA at year 6 was significantly lower in non-reimbursed areas than in reimbursed areas (52.1 vs 64.6 letters, $p < 0.01$). Change in BCVA at year 6 from year 2 was − 2.4 (combination, reimbursed), − 5.5 (monotherapy, reimbursed), − 12.8 (monotherapy, non-reimbursed), − 18.0 letters (combination, non-reimbursed), reimbursed vs non-reimbursed $p < 0.01$; combination vs monotherapy $p = 0.41$ in non-reimbursed areas; $p = 0.53$ in reimbursed


A
68.2
67.9
65.6
P=0.92
63.0
P=0.36
58.5
56.8
P=0.70
Initial Study (EVEREST II)
Visual acuity, letters
Time, years
Monotherapy
Combination
B
Baseline
Year 2
Year 6
45%
43%
50%
53%
5%
4%
65%
63%
30%
53%
5%
8%
34%
29%
49%
53%
17%
19%
monotherapy
combination
Good visual acuity (≥69 letters)
Moderate visual acuity (68-36 letters)
Poor visual acuity (<36 letters)
C
Proportion of eyes with ≥15 letter gain
Proportion of eyes with ≥15 letter loss
13%
16%
8%
2%
5%
4%
33%
38%
Year 0 - 2
Year 0 - 6
monotherapy
combination

◀**Fig. 2** Visual outcomes from baseline to year 6. **a** Comparison of best-corrected visual acuity (BCVA) between the combination and monotherapy arms as per initial randomization from the EVEREST trial. BCVA is observed to improve over the initial EVEREST II trial period (0–2 years) as per reported in the original study. There was a drop in BCVA from year 2 to 6 (as plotted as a LOESS regression curve). BCVA was not significantly different at each time point. **b** Proportion of eyes with good (≥ 69 letters), moderate (68–36 letters), and poor visual acuity (< 36 letters) at baseline, year 2, and year 6. The highest proportion of good vision was observed at year 2 with a reduction in this proportion at year 6. **c** Proportion of eyes with ≥ 15 letter gain and loss compared between the combination arm and monotherapy arm at year 2 and year 6. There was no significant difference in proportion of eyes that gained or loss ≥ 15 letter between arms at either time point

areas. A significantly higher proportion of eyes from non-reimbursed areas lost ≥ 15 letters at year 6 compared to reimbursed areas (42.0% vs 18.4%, $p < 0.03$) (Table 6). Comparison of year 2–6 treatment exposure between reimbursed and non-reimbursed countries showed that a numerically higher proportion of eyes received treatment (84.6% vs 68.6%, $p = 0.08$), a higher mean number of anti-VEGF (9.1 vs 6.1, $p < 0.01$) but a similar number of visits (16.4 vs 17.6, $p = 0.61$).

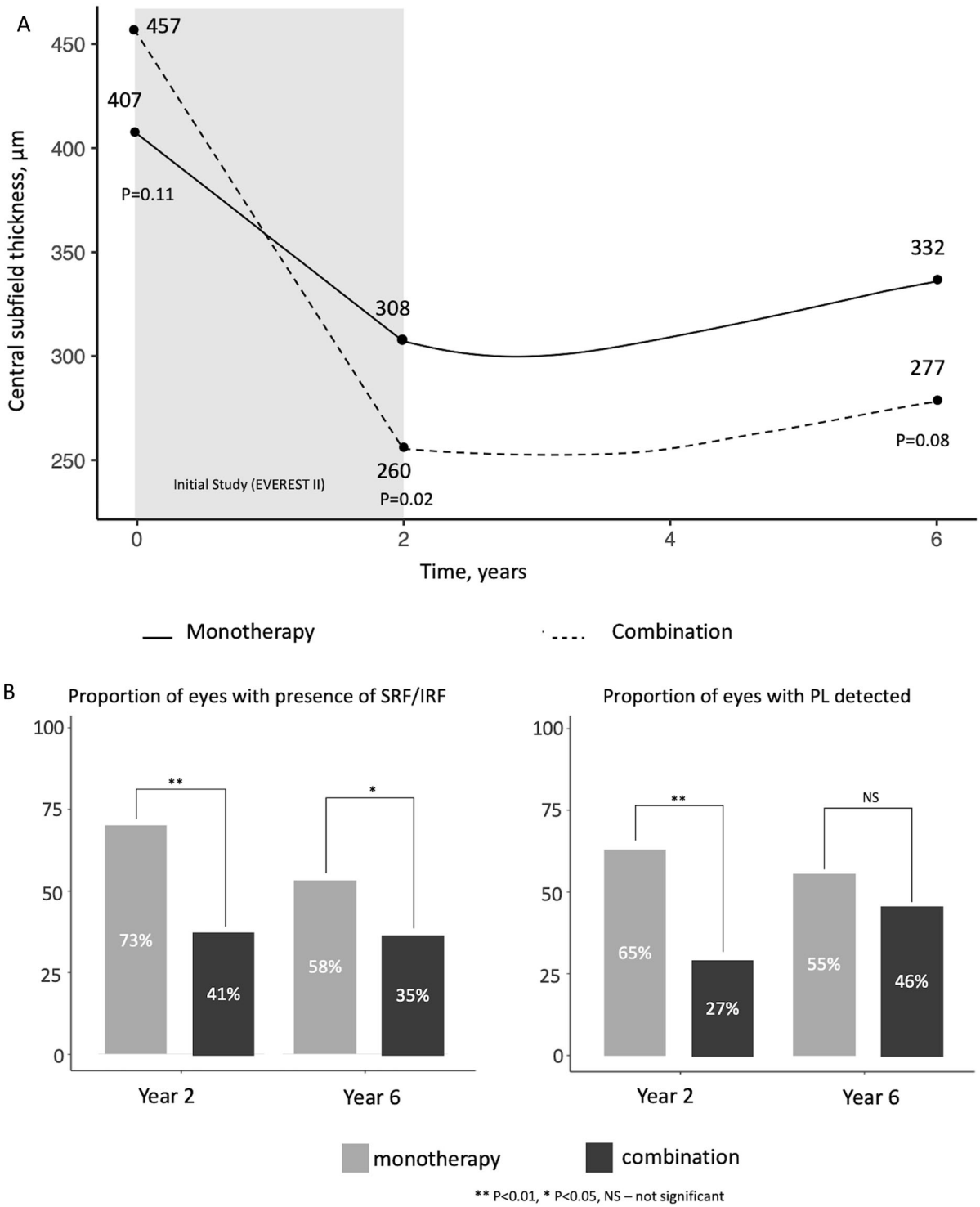
Adverse Events

Three adverse events were reported, including one case of submacular hemorrhage, one case of raised intraocular pressure post intravitreal injection, and one case of vomiting after angiography.

DISCUSSION

In the current study, we invited participants who completed the 2-year EVEREST II study for an examination at 6 years after enrolment to assess the functional and anatomical outcomes, and the re-treatment needs beyond 2 years. The 6-year follow-up group comprised roughly one-third of all completers from seven countries, with 45.5% having been in the monotherapy arm and 54.5% having been in the combination arm. While we recognize that the low participation rate may result in recall bias, this is a common challenge in long-term follow-up studies. For example in the SEVEN-UP study, the long-term 7- to 8-year follow-up study of the landmark ANCHOR [17], MARINA [18], and HORIZON [19] trials, only about 40% of patients who were eligible for the long-term study participated [1]. Despite this, our current study provides valuable insights into the long-term outcomes of treatment for PCV which is not feasible in a randomized controlled trial design.

After exiting from the EVEREST II study, patients were followed up and treated according to standard of care in their respective area. The observations at 6 years represent the combination of treatments received during the trial and the post-trial management. The purpose of this analysis is a description of the treatment patterns for patients with PCV in clinical practice rather than to compare the initial treatment arms and their long-term effects. One of the key findings was the ability to observe differences in outcomes between different healthcare settings. We note that the majority of patients in the follow-up cohort received additional treatments between year 2 and year 6, and among those initially randomized to monotherapy, one-third received PDT after exiting the EVEREST II study. Compared to the overall cohort, the 6-year follow-up participants had higher baseline BCVA (mean 68.4 letters [monotherapy], 69.7 letters [combination]). In keeping with the overall EVEREST II study, BCVA gain was higher in the combination group at 2 years (+ 5.2 vs + 2.3 letters) [8]. However, at year 6, BCVA dropped in both groups to below baseline (58.6 letters [monotherapy], 56.8 letters [combination], $p = 0.701$). At year 6, about one-third of eyes had good vision (BCVA ≥ 69 letters) and about almost one-fifth of eyes had very poor vision (BCVA < 36 letters). Fewer eyes had SRF/IRF in the combination group than monotherapy group, while about half had detectable PL in both groups, regardless of initial randomization group. These results suggest recurrence is common in PCV, regardless of initial therapy. In


A
457
407
P=0.11
308
260
P=0.02
332
277
P=0.08
Initial Study (EVEREST II)
Central subfield thickness, µm
Time, years
Monotherapy
Combination
B
Proportion of eyes with presence of SRF/IRF
73%
41%
58%
35%
Year 2
Year 6
Proportion of eyes with PL detected
65%
27%
55%
46%
NS
monotherapy
combination
** P<0.01, * P<0.05, NS – not significant

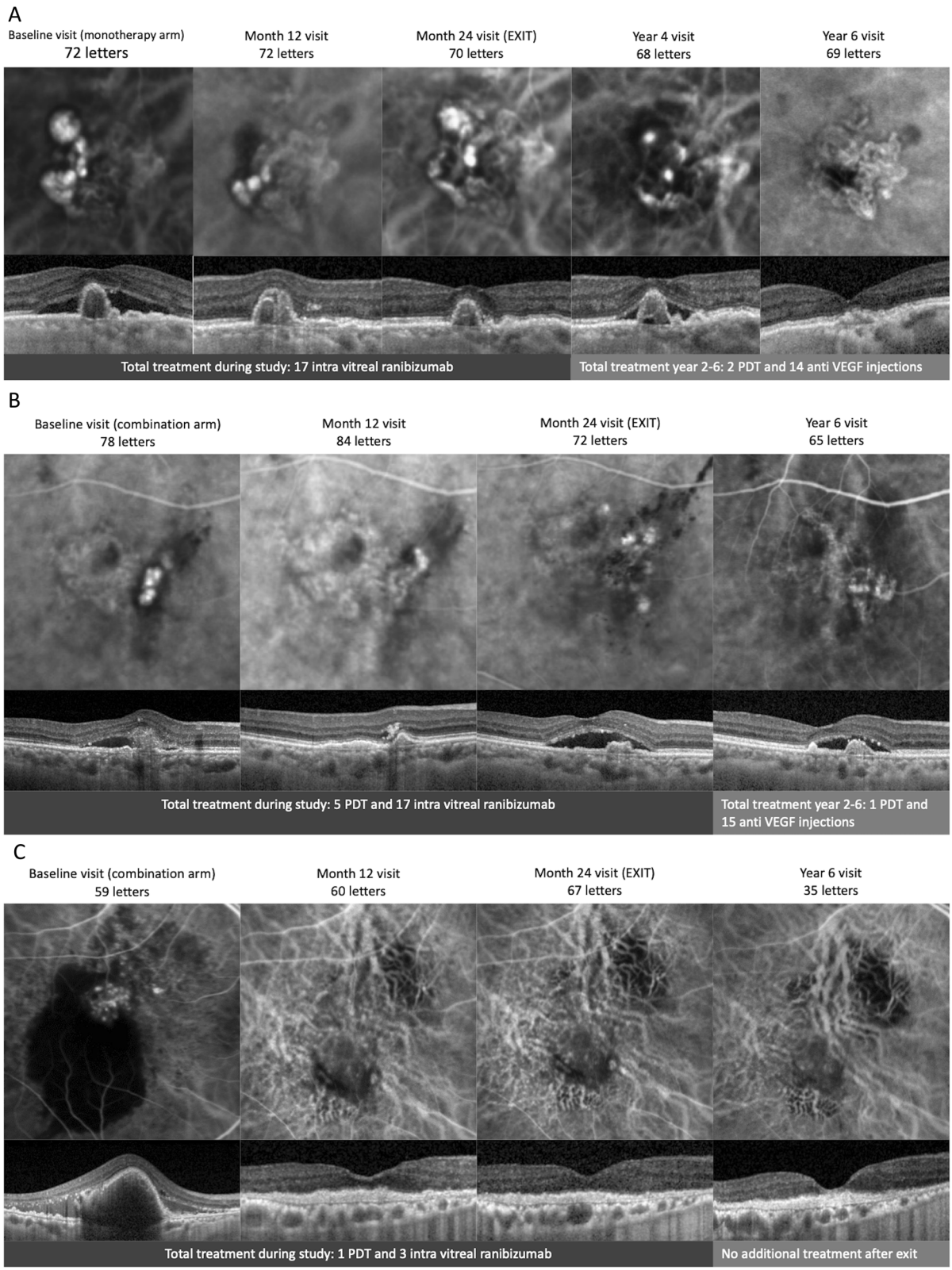
◀**Fig. 3** Anatomical outcomes from baseline to year 6. **a** Comparison of central subfield thickness (CST) between the combination and monotherapy arms as per initial randomization from the EVEREST trial. A reduction in CST is observed over the initial EVEREST II trial period (0–2 years) as per reported in the original study. The CST remained fairly constant through year 2–6 (as plotted as a LOESS regression curve). CST was only significantly different at year 2 (at the conclusion of the initial EVEREST study). **b** Proportion of eyes with the presence of SRF/IRF and PL. There were significantly fewer eyes with SRF/IRF in the combination arm compared to the monotherapy arm at year 2 and 6. There were significantly fewer eyes with PL lesions detected at year 2 (consistent with the original EVEREST II study) in the combination arm compared to the monotherapy arm. At year 6 the numbers of eyes with PL lesions were similar

keeping with the high proportion of eyes with presence of SRF/IRF, 75.5% (monotherapy group) and 75.6% (combination group) eyes reported having received additional treatments after exiting the 2-year EVEREST II study, and one-third of eyes initially randomized to monotherapy received PDT after exiting EVEREST II.

In comparing initial monotherapy versus combination, we did not find significant difference in BCVA at year 6. However, initial combination was associated with superior anatomical outcome at year 6 and fewer anti-VEGF re-treatments compared to eyes initially randomized to monotherapy, suggesting initial combination may have a legacy effect on anatomical control while maintaining the similar long-term vision. Comparison between eyes that received any PDT over the 6-year period to those who never received PDT also showed similar visual but better anatomical outcomes with fewer anti-VEGF treatments at year 6. There were numerically more eyes that developed fibrosis and atrophy following any PDT, but the difference was not statistically significant. It is interesting to note that while the anti-VEGF treatment number was lower in the combination group, the mean number of visits was similar (16.9 monotherapy group, 17.2 combination group over 4 years). This may reflect physicians' tendency to monitor patients on a quarterly basis.

Factors associated with BCVA at year 6 include BCVA (year 2), CST (year 2), presence of SRF/IRF at year 2, and number of anti-VEGF (year 2–year 6). Figure 4 shows representative imaging of patients from the initial EVEREST II study and the factors associated with year 6 outcomes. The only factor associated with PL closure at year 6 was PL closure at year 2. At year 6, however, the proportion of eyes with PL closure had decreased in the combination arm and the difference between arms was no longer statistically significant. PL closure per se at year 2 was not associated with final BCVA or presence of SRF/IRF at year 6. These results suggest that PL closure does not directly translate into better BCVA or lower proportion with presence of SRF/IRF in the long term. Hence the treatment should aim to control any exudation from either the PL and/or branching vascular network instead of focusing on closure of PL.

The most notable difference in visual outcomes was observed in the comparison between reimbursed and non-reimbursed countries, which showed that patients from non-reimbursed countries lost on average 10 more letters than their counterparts in reimbursed countries. This difference was observed regardless of initial randomization arm: in reimbursed areas, BCVA decline was mild (2.4 letters [combination]; 5.5 letters [monotherapy]) whereas in non-reimbursed areas BCVA declined markedly (12.8 letters [monotherapy] to 18.0 letters [combination]). After exiting the EVEREST II study, patients were treated according to the standard of care. We observed a higher proportion of patients receiving re-treatment and higher number of anti-VEGF injections in reimbursed countries. These findings suggest


A
Baseline visit (monotherapy arm)
72 letters
Month 12 visit
72 letters
Month 24 visit (EXIT)
70 letters
Year 4 visit
68 letters
Year 6 visit
69 letters
Total treatment during study: 17 intra vitreal ranibizumab
Total treatment year 2-6: 2 PDT and 14 anti VEGF injections
B
Baseline visit (combination arm)
78 letters
Month 12 visit
84 letters
Month 24 visit (EXIT)
72 letters
Year 6 visit
65 letters
Total treatment during study: 5 PDT and 17 intra vitreal ranibizumab
Total treatment year 2-6: 1 PDT and 15 anti VEGF injections
C
Baseline visit (combination arm)
59 letters
Month 12 visit
60 letters
Month 24 visit (EXIT)
67 letters
Year 6 visit
35 letters
Total treatment during study: 1 PDT and 3 intra vitreal ranibizumab
No additional treatment after exit

◀**Fig. 4** Representative examples of imaging for patients from commencement of EVEREST II study to year 6. The visit and corresponding best-corrected visual acuity (BCVA) is indicated on the top and a summary of treatment on the bottom of each panel of images (**a–c**). **a** Imaging from a patient that had good outcomes at year 6. The indocyanine green angiography (ICGA) (top row) shows the a large cluster of polypoidal lesions (PL) at baseline which persisted till year 4. The PL eventually resolved at year 6. Disease activity as observed on OCT (bottom row) was well controlled over the course of the EVEREST II study with resolution of all sub- and intraretinal fluid at year 2 (exit of EVEREST II study). The patient also received 14 anti-VEGF injections and 2 subsequent PDTs from year 2 to 6. Final BCVA was good, with features consistent with the factors associated with good final BCVA such as no fluid at year 2 and consistent treatment with anti-VEGF from year 2 to 6. **b** Imaging from a patient with moderate outcomes at year 6 with a persistently active lesion. The ICGA (top row) shows persistent PL through the course of treatment. The PL eventually resolved at year 6. Despite a high number of treatments over the EVEREST II study and from year 2 to 6, disease activity was persistent as observed as SRF on OCT (bottom row). The findings of this patient are consistent with the association between OCT fluid status at year 2 and at year 6. This patient eventually had a moderate level of vision with BCVA of 65 letters at year 6. **c** Imaging from a patient with poor outcomes at year 6. The ICGA (top row) shows resolution of PL after initial PDT; however, despite the paucity of fluid on OCT (bottom row), visual acuity appeared to steadily decline from the development of subretinal fibrosis resulting in the thinning and loss of ellipsoid zone at the fovea on OCT at year 6

that the reimbursement system may contribute to differences in outcomes, possibly through differences in re-treatment intensity as we noticed a higher number of anti-VEGF treatments in the reimbursed countries compared to non-reimbursed countries. While it appears that financial burden may be a significant driving factor for better vision in the reimbursed countries, other factors such as access to care, patients' understanding of the disease, and treatment fatigue may also contribute to these differences in outcomes. Differences in treatment protocols and re-treatment criteria between countries or even individual practice may also have played a role. Unfortunately treatment regimen is highly heterogeneous between different settings, and we do not have data to analyze the effect of this.

Strengths of this study include the relatively long follow-up, relatively balanced distribution of randomization arms among patients who participated in the follow-up study, inclusion of participants from seven countries, the ability to obtain re-treatment data from medical records in addition to patient recall, and the ability to match the year 6 data with initial randomization arm. Limitations should be mentioned. The follow-up population only represented about 40% of the 2-year completers. Selection bias is inherent to this kind of long-term follow-up. The sample size in each group was limited and comparisons are underpowered. The current results summarize the findings at year 6 but do not allow a detailed understanding of the reasons for and timing of changes between year 2 and year 6. The lower number of re-treatments could be due to treatment success or futility. Similarly, poor outcome may be due to undertreatment or simply late presentation. Furthermore, treatment standards may vary from country to country. To better understand the reasons behind the deterioration in those with vision loss, we will perform a detailed analysis of treatment patterns and temporal changes in our next manuscript. Finally, these results may not apply to treatment with anti-VEGF agents other than ranibizumab.

CONCLUSIONS

In summary, we observed no difference in visual outcomes between initial treatment arms although initial combination therapy was associated with better anatomic outcomes and fewer injections. However, regardless of initial treatment, it is possible to maintain relatively good vision in about a third patients with PCV over 6 years, especially in those that were more frequently treated. To achieve good visual outcome, early control of disease followed by long-term monitoring and adequate and timely re-treatment are recommended, regardless of whether polypoidal lesions have been closed.

Table 5 Factors associated with anatomical outcomes

	Presence of SRF/IRF						Presence of PL			
	No	Yes	OR univariable	*p*	OR multivariable	*p*	No	Yes	OR univariable	*p*
Age, mean (SD)	69.4 (6.3)	68.4 (6.1)	0.97 (0.90–1.04)	0.46	–		69.8 (6.7)	68.5 (5.7)	0.97 (0.90–1.04)	0.34
Gender, male	33 (52.4)	30 (47.6)	1.52 (0.59–4.09)	0.39	–		31 (49.2)	32 (50.8)	1.12 (0.44–2.85)	0.81
Initial treatment arm, combination	31 (64.6)	17 (35.4)	0.42 (0.18–0.99)	0.03	0.45 (0.21–0.99)	0.03	26 (54.2)	22 (45.8)	0.69 (0.30–1.60)	0.39
BCVA (baseline), letters, mean (SD)	6.2 (1.6)	6.7 (1.1)	1.35 (0.98–1.94)	0.08	–		6.4 (1.4)	6.4 (1.4)	1.02 (0.75–1.38)	0.92
BCVA (year 2), letters, mean (SD)	6.6 (1.4)	7.2 (1.2)	1.49 (1.04–2.31)	0.02	1.53 (1.01–2.32)	0.04	6.8 (1.3)	6.9 (1.4)	1.10 (0.80–1.54)	0.57
CST (baseline), µm, mean (SD)	4.5 (1.6)	4.2 (1.3)	0.87 (0.64–1.17)	0.38	–		4.6 (1.5)	4.1 (1.4)	0.79 (0.57–1.07)	0.14
CST (year 2), µm, mean (SD)	2.7 (0.9)	3.0 (1.1)	1.40 (0.90–2.29)	0.15	–		2.9 (1.1)	2.7 (0.9)	0.76 (0.47–1.19)	0.25
Total anti-VEGF (year 2–6), mean (SD)	6.6 (7.4)	9.7 (8.2)	1.05 (1.00–1.12)	0.08	–		7.7 (7.9)	8.6 (8.0)	1.01 (0.96–1.07)	0.60
Total PDT (year 2–6), mean (SD)	0.5 (0.8)	0.5 (0.9)	1.08 (0.65–1.78)	0.76	–		0.4 (0.8)	0.6 (0.9)	1.34 (0.81–2.31)	0.27
Presence of SRF/IRF at year 2	21 (43.8)	27 (56.2)	2.89 (1.21–7.20)	0.02	2.59 (0.99–6.74)	0.04	27 (56.2)	21 (43.8)	0.54 (0.23–1.27)	0.16
Presence of polyps at year 2	17 (45.9)	20 (54.1)	1.92 (0.81–4.61	0.14	–		12 (31.6)	26 (68.4)	3.73 (1.55–9.41)	< 0.01

Table 6 Comparison between reimbursed and non-reimbursed areas

	Non-reimbursed (N = 50)	Reimbursed (N = 38)	p
BCVA			
Baseline, letters, mean (SD)	63.2 (13.4)	65.5 (14.5)	0.54
Year 2, letters, mean (SD)	67.9 (13.9)	68.3 (14.6)	0.91
Year 6, letters, mean (SD)	52.1 (23.9)	64.6 (13.0)	< 0.01
BCVA change from baseline			
Year 2, letters, mean (SD)	+ 4.7 (11.2)	+ 2.8 (9.6)	0.39
Year 6, letters, mean (SD)	− 11.0 (25.9)	− 1.0 (15.8)	0.04
Year 2, ≥ 15 letters loss, *n* (%)	2 (4.0%)	2 (5.3%)	1.00
Year 6, ≥ 15 letters loss, *n* (%)	21 (42.0%)	7 (18.4%)	0.03
Central subfield thickness, mm			
Baseline, mm	441.9 (144.5)	424.4 (148.8)	0.58
Year 2, mm	290.7 (114.2)	268.9 (72.6)	0.31
Year 6, mm	308.8 (169.1)	292.9 (110.9)	0.62
CST change			
Year 2, mm	− 151.2 (160.4)	− 130.0 (193.9)	0.94
Year 6, mm	− 133.1 (200.9)	− 179.9 (209.5)	0.01
Presence of SRF/IRF			
Year 2, *n* (%)	30 (58.8)	15 (39.5)	0.54
Year 6, *n* (%)	25 (50.0)	19 (50.0)	0.44
Presence of polyps			
Year 2, *n* (%)	21 (41.2)	18 (47.7)	0.71
Year 6, *n* (%)	22 (55.0)	22 (45.8)	0.52
Presence of fibrosis at year 6, *n* (%)	14 (27.5)	3 (7.7)	0.04

Table 6 continued

	Non-reimbursed ($N = 50$)	Reimbursed ($N = 38$)	*p*
Presence of atrophy at year 6, *n* (%)	5 (9.8)	1 (2.6)	0.35
Received treatment year 2–6, *n* (%)	35 (68.6)	33 (84.6)	0.08
Number of visits year 2–6, *n* (%)	17.6 (9.9)	16.4 (11.7)	0.61
Total anti-VEGF year 2–6, *n* (%)	6.1 (3.2)	9.1 (4.3)	< 0.01
Total PDT year 2–6, *n* (%)	0.6 (1.0)	0.4 (0.6)	0.31

Author Contribution. All authors contributed to data collection and critical review of the manuscript. Dr. Teo and Dr Cheung contributed to concept and design, statistical analysis and drafting the manuscript. We would like to acknowledge Divya D'Souza and Kinfemichael Gedif for supporting data management.

Funding. Sponsorship for this study was funded by National Medical Research Council Singapore Open Fund Large Collaborative Grant: NMRC/LCG/004/2018. No funding or sponsorship was received for the publication of this article.

Data Availability. All data analyzed during this study are included in this published article.

Declarations

Conflict of Interest. Dr. Teo reports consultancy fees, honorarium, travel support and speaker fees from Bayer and Novartis outside the submitted work. Dr. Park reports consultancy fees, honorarium, travel support and speaker fees from Bayer, Novartis, Alcon, Roche, Samsug Bioepis, Oculight, RetiMark outside the submitted work. Dr. Ruamviboonsuk reports consultancy fees, grants, travel support and speaker fees from Roche and Bayer outside the submitted work. Dr Mori reports personal fees from Bayer Yakuhin Ltd., Chugai Pharmaceutical Co, Ltd., Novartis Pharma K.K., Senju Pharmaceutical Co, Ltd., Santen Pharmaceutical Co, Ltd, and Nippon Boehringer Ingelheim Co, Ltd. Dr. Chen SJ reports consultation fees from Roche, Bayer, Novartis and Allergan outside the submitted work. Dr. Lee reports consultancy fees, travel support and speaker fees from Bayer, Novartis, Roche outside the submitted work. Dr. Rajagopalan reports honorarium, grants and speaker fees from Alcon, Allergan, Bayer, Novartis and Roche outside the submitted work. Dr. Terasaki reports research support for instrument from Carl Zeiss and speaker fees from Alcon, Bayer, Novartis, Santen, Chugai and Sanofi outside the submitted work. Dr. Sekiryu reports support from Santen, Senju, Chugai, Alcon, Novartis,

and Bayer outside the submitted work. Dr. Yanagi reports honorarium, grants and speaker fees from Alcon, Bayer, Boehringer Ingelheim, Kyowa Kirin, Novartis, Santen Pharmaceuticals, Senju Pharmaceuticals and Roche/Chugai outside the submitted work. Dr. Lai reports consultancy fees, grants, travel support and speaker fees from Bayer, Novartis and Roche during the conduct of the study; consultancy fees, grants and speaker fees from Bayer, Novartis and Roche outside the submitted work. Dr. Cheung reports consultancy fees, honorarium, travel support and speaker fees from Bayer, Novartis, Roche, Boehringer Ingelheim, Zeiss and Topcon outside the submitted work.

Ethical Approval. The study was conducted in accordance with the tenets of the Declaration of Helsinki and with approval of respective institutional review boards of the participating centers.

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