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# Efficacy and Safety of Ranibizumab With or Without Verteporfin Photodynamic Therapy for Polypoidal Choroidal Vasculopathy
## A Randomized Clinical Trial

Adrian Koh, MD, FRCS; Timothy Y. Y. Lai, MD, FRCS; Kanji Takahashi, MD; Tien Y. Wong, MD, PhD; Lee-Jen Chen, MD; Paisan Ruamviboonsuk, MD; Colin S. Tan, FRCS(ED); Chrystel Feller, PhD; Philippe Margaron, PhD; Tock H. Lim, FRCS (ED); Won Ki Lee, MD, PhD; for the EVEREST II study group

**IMPORTANCE** Polypoidal choroidal vasculopathy (PCV) is a common subtype of exudative age-related macular degeneration among Asian individuals. To our knowledge, there are no large randomized clinical trials to evaluate intravitreal ranibizumab, with and without verteporfin photodynamic therapy (vPDT), for the treatment of PCV.

**OBJECTIVE** To compare the efficacy and safety of combination therapy of ranibizumab and vPDT with ranibizumab monotherapy in PCV.

**DESIGN, SETTING, AND PARTICIPANTS** A double-masked, multicenter randomized clinical trial of 322 Asian participants with symptomatic macular PCV confirmed by the Central Reading Center using indocyanine green angiography was conducted between August 7, 2013, and March 2, 2017.

**INTERVENTIONS** Participants were randomized 1:1 to ranibizumab, 0.5 mg, and vPDT (n = 168; combination therapy group) or ranibizumab, 0.5 mg, and sham PDT (n = 154; monotherapy group). All participants received 3 consecutive monthly ranibizumab injections, followed by a pro re nata regimen. Participants also received vPDT/sham PDT on day 1, followed by a pro re nata regimen based on the presence of active polypoidal lesions.

**MAIN OUTCOMES AND MEASURES** Step 1 assessed whether combination therapy was noninferior (5-letter margin) to monotherapy for change in best-corrected visual acuity from baseline and superior in complete polyp regression. If noninferiority was established, step 2 assessed whether combination therapy was superior to monotherapy measured by best-corrected visual acuity change at month 12.

**RESULTS** Baseline demographics of the 322 participants were comparable between the treatment groups. Mean (SD) age of the patients was 68.1 (8.8) years, and overall, 69.9% of the patients were men. At baseline, the overall mean best-corrected visual acuity and mean central subfield thickness were 61.1 letters and 413.3 µm, respectively. At 12 months, mean improvement from baseline was 8.3 letters with combination therapy vs 5.1 letters with monotherapy (mean difference, 3.2 letters; 95% CI, 0.4-6.1), indicating that combination therapy met the predefined criterion for noninferiority as well as being superior to monotherapy ($P$ = .01). Combination therapy was also superior to monotherapy in achieving complete polyp regression at month 12 (69.3% vs 34.7%; $P$ < .001). Over 12 months, the combination therapy group received a median of 4.0 ranibizumab injections compared with 7.0 in the monotherapy group. Vitreous hemorrhage was the only ocular serious adverse event (combination therapy group, 1 [0.6%]; monotherapy group, 3 [2.0%]).

**CONCLUSIONS AND RELEVANCE** After 12 months, combination therapy of ranibizumab plus vPDT was not only noninferior but also superior to ranibizumab monotherapy in best-corrected visual acuity and superior in complete polyp regression while requiring fewer injections. Combination therapy should be considered for eyes with PCV.

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**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** The members of the EVEREST II study group are listed at the end of this article.

**Corresponding Author:** Adrian Koh Hock Chuan, MD, FRCS, Eye and Retina Surgeons, 13-03 Camden Medical Centre, 1 Orchard Boulevard, Singapore 248649 (ak@ers.clinic).

Polypoidal choroidal vasculopathy (PCV) is an exudative retinal disease characterized by an abnormal subretinal pigment epithelial network of vessels of choroidal origin, ending in aneurysmal dilatations, which appear as spheroidal polyplike structures.[1] Hemorrhage and exudation from this vascular network can lead to chronic, multiple, recurrent serosanguineous detachments of the retinal pigment epithelium and retina.[1,2] Untreated, the long-term prognosis of PCV is poor.[3]

The pathogenesis of PCV remains unclear; it was initially considered a distinct abnormality of the inner choroidal vasculature[2]; however, the histopathological evidence suggests that PCV is a variant of type I or occult choroidal neovascularization seen in neovascular age-related macular degeneration (nAMD), located above or within the Bruch membrane.[4-6] Furthermore, studies within the past decade show that systemic and genetic risk factors for PCV and typical nAMD appear to be fairly similar.[7-9] Thus, PCV is considered one of the subtypes of nAMD.[1,10,11]

Indocyanine green angiography (ICGA) is essential for accurately diagnosing PCV, helping to visualize the hyperfluorescent polypoidal lesions.[10,12,13] In general, PCV is reported to be more prevalent in certain racial/ethnic groups, especially in Asian individuals, where the proportion of PCV among nAMD cases varies from 22.3% to 61.6%.[4,14,15] However, with increased use of ICGA and advances in other diagnostic techniques,[12,13] a rise in the frequency of PCV diagnosis has been observed across all patient populations.[4,16-18]

The anti-vascular endothelial growth factor agent ranibizumab, with or without verteporfin photodynamic therapy (vPDT), has shown efficacy in improving visual outcomes and diminishing polypoidal lesions in patients with PCV.[10,19,20] The EVEREST study was a randomized clinical trial in 61 participants that showed that combination therapy was significantly superior to ranibizumab monotherapy in achieving complete polyp regression over 6 months.[19] Although best-corrected visual acuity (BCVA) also improved in participants treated with either combination therapy or ranibizumab monotherapy, the study was not powered to compare the effects of these treatment modalities on BCVA gains and did not evaluate results beyond 6 months.[19] Therefore, we conducted the 24-month EVEREST II trial to compare the long-term effect of combination therapy vs ranibizumab monotherapy in a large Asian patient population with symptomatic macular PCV. Here, we report the 12-month primary and secondary outcomes.

### Key Points

**Question** Are there any differences in treatment outcomes between combination therapy with intravitreal ranibizumab and verteporfin photodynamic therapy compared with ranibizumab monotherapy in polypoidal choroidal vasculopathy?

**Findings** In the multicenter EVEREST II randomized clinical trial, compared with ranibizumab monotherapy, treatment of polypoidal choroidal vasculopathy with ranibizumab plus verteporfin photodynamic therapy resulted in greater visual acuity improvement (8.3 vs 5.1 letters) than monotherapy and complete resolution of lesions with fewer ranibizumab injections.

**Meaning** These data suggest ranibizumab plus verteporfin photodynamic therapy should be considered for treatment of eyes with polypoidal choroidal vasculopathy.

## Methods

### Study Design

The EVEREST II trial was a 24-month multicenter, randomized, double-masked study designed to compare the efficacy and safety profile of ranibizumab, 0.5 mg, and vPDT combination therapy with ranibizumab, 0.5 mg, monotherapy in participants with symptomatic macular PCV from Hong Kong, Japan, South Korea, Malaysia, Singapore, Taiwan, and Thailand. The study was conducted in accordance with the Declaration of Helsinki and Tripartite International Council on Harmonization Good Clinical Practice Guidelines and applicable local regulations. The study protocol was reviewed and approved by an independent ethics committee or institutional review board at each center. All participants provided written informed consent. The trial protocol and statistical analysis plan are available in Supplement 1.

### Participants

The study population consisted of treatment-naive participants 18 years and older with symptomatic macular PCV, as defined by the presence of active macular polypoidal lesions on ICGA and by the presence of serosanguineous maculopathy on color fundus photography and fluorescein angiography. The presence of PCV in 1 study eye and eligibility for enrollment were confirmed by the Central Reading Center (Fundus Image Reading Centre, Singapore) using a standardized reading protocol using well-defined grading criteria as in EVEREST.[12,19] The eligible BCVA letter score range was between 78 and 24 (approximately 20/32 to 20/320 Snellen equivalent), measured using Early Treatment Diabetic Retinopathy Study visual acuity charts at 4 m following refraction.

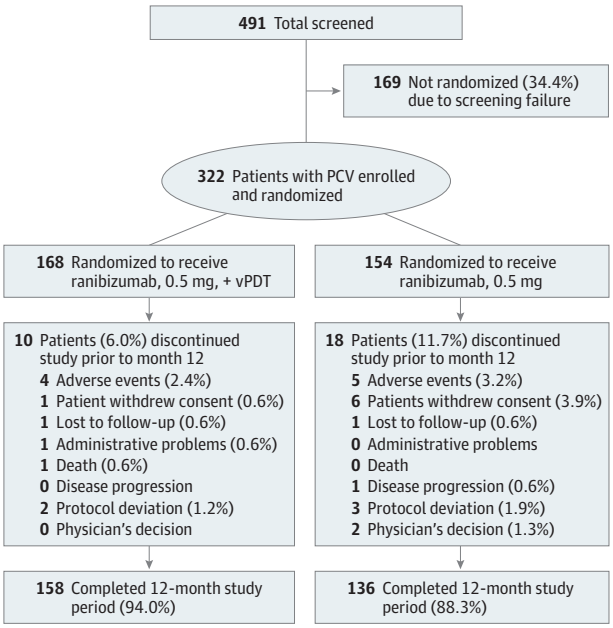
Details of the patient inclusion and exclusion criteria are listed in the eMethods in Supplement 2.

### Randomization and Treatment

Participants, evaluating investigators, vision examiners, and Central Reading Center graders were masked to the treatment. Separate unmasked investigators (treating physicians) performed the treatments. All eligible participants were randomized 1:1 to either combination therapy with ranibizumab, 0.5 mg, and standard fluence vPDT or ranibizumab, 0.5 mg, monotherapy (with sham PDT). Randomization was balanced by site (eMethods in Supplement 2).

All participants were assessed monthly. An intravitreal ranibizumab injection (0.5 mg/0.05 mL) was administered on day 1 (baseline) and at months 1 and 2, followed by a pro re nata (PRN) regimen according to the protocol-specific retreatment criteria, with at least a 28-day interval between 2 ranibizumab treatments (eMethods and eFigure 1 in Supplement 2). On day 1, participants in the combination group were infused with intravenous verteporfin (6 mg/m$^2$), and those in the

Figure 1. Patient Disposition (Randomized Set)




Randomized set consisted of all randomized participants. Percentages are based on the total number of participants in the randomized set in the respective treatment groups. The 5 participants discontinued from the study owing to protocol deviation were enrolled before the Central Reading Center confirmed polypoidal choroidal vasculopathy (PCV) diagnosis. One of the 2 participants whom the physician decided to withdraw did not respond to treatment and the primary investigator decided to change the treatment. In the other case, there were no documented reasons but the participant did not experience any adverse events. Spectral-domain optical coherence tomography, color fundus photography, fluorescein angiography, and indocyanine green angiography were assessed by the Central Reading Center.

monotherapy group were infused with 5% dextrose solution. Fifteen minutes after the start of infusion, laser (light dose, 50 J/cm$^2$; dose rate, 600 mW/cm$^2$; wavelength, 689 nm) was applied onto the whole lesions in the study eye for 83 seconds. Photodynamic therapy tubing was covered with foil or a blanket. Thereafter, vPDT or sham PDT was administered on a PRN basis from month 3 onwards per the protocol-specific retreatment criteria (eMethods and eFigure 1 in Supplement 2), with at least a 3-month interval between 2 vPDT or sham PDT treatments. As per protocol criteria, fellow eyes that developed macular pathologies were appropriately treated (Trial Protocol in Supplement 1).

## Study Objectives

The primary objectives were to demonstrate that combination therapy was (1) noninferior to ranibizumab monotherapy in participants with symptomatic macular PCV with respect to change in BCVA (Early Treatment Diabetic Retinopathy Study letters) from baseline to month 12 with a predefined noninferiority margin of 5 letters and (2) superior with respect to complete polyp regression as assessed by ICGA at month 12. Once this was established, the next step was to show the superiority of combination therapy vs ranibizumab monotherapy with respect to BCVA change from baseline to month 12. The secondary objectives included additional functional and anatomical outcomes, treatment exposure, and safety and tolerability for both treatments up to month 12.

### Efficacy Assessments

Efficacy assessments included both functional (BCVA) and multimodal image (ICGA, fluorescein angiography, color fundus, and spectral-domain optical coherence tomography) evaluations of the study eye. Disease activity was assessed based on BCVA loss, spectral-domain optical coherence tomography, ICGA, fluorescein angiography, and color fundus anomalies (eMethods in Supplement 2).

### Safety Assessments

Adverse events (AEs) were assessed at each visit.

## Statistical Analysis

A sample size of 160 participants per treatment group was estimated to appropriately power the prespecified primary analysis, with the combined power to achieve a 1-sided noninferiority margin of 5 letters between combination therapy and ranibizumab monotherapy with respect to the BCVA change from baseline to month 12, superiority with respect to complete polyp regression, and superiority with respect to BCVA change from baseline at the 1-sided level of $\alpha = .025$ was at least 87.0%.

The primary efficacy objective was tested based on an analysis of covariance model including treatment group as a factor and (centered) baseline BCVA as a continuous variable for testing noninferiority/superiority of BCVA change from baseline and on a Fisher test to evaluate for superiority with respect to complete polyp regression (eMethods in Supplement 2). The multiple 1-sided $\alpha$-level of .025 was to be maintained by applying a sequentially rejecting multiple testing procedure (steps 1 and 2).

Baseline demographics and disease characteristics are presented using descriptive statistics. The primary analysis was conducted on the full analysis set (FAS) using the last observation carried forward approach for imputation of the missing data. The FAS comprised all participants who were assigned to a treatment regimen. The secondary analyses were conducted on the study eye of participants in the FAS. The safety analysis was descriptive and conducted on the safety set that consisted of all participants who received at least 1 application of study treatment and had at least 1 postbaseline safety assessment.

# Results

## Patient Disposition and Baseline Characteristics

In total, 322 participants were randomized to receive combination therapy (n = 168) or ranibizumab monotherapy (n = 154; **Figure 1**). Five participants without active polypoidal lesions were randomized in error before Central Reading Center confirmation.

Baseline characteristics were comparable between groups. Overall, the mean (SD) age of participants was 68.1 (8.8) years, and most participants were men (69.9%; **Table**). The mean

Table. Patient Demographics, Baseline Disease, and Ocular Characteristics (Randomized Set)

| Parameter | No. (%)[a] | |
|---|---|---|
| | Ranibizumab, 0.5 mg, + vPDT (n = 168) | Ranibizumab, 0.5 mg (n = 154) |
| Age, y | | |
| No. | 168 | 154 |
| Mean (SD) | 68.0 (8.5) | 68.2 (9.0) |
| Age category, y | | |
| <50 | 0 | 4 (2.6) |
| 50-<65 | 57 (33.9) | 53 (34.4) |
| 65-<75 | 73 (43.5) | 56 (36.4) |
| 75-<85 | 33 (19.6) | 34 (22.1) |
| ≥85 | 5 (3.0) | 7 (4.5) |
| Sex | | |
| Male | 109 (64.9) | 116 (75.3) |
| Female | 59 (35.1) | 38 (24.7) |
| Race/ethnicity | | |
| Chinese | 64 (38.1) | 59 (38.3) |
| Indian (Indian subcontinent) | 3 (1.8) | 2 (1.3) |
| Japanese | 46 (27.4) | 38 (24.7) |
| Other | 55 (32.7) | 55 (35.7) |
| BCVA letter score | | |
| No. | 168 | 153 |
| Mean (SD) | 61.1 (12.6) | 61.2 (13.9) |
| Categorized BCVA letter score (approximate Snellen equivalent) | | |
| <39 (Worse than 20/160) | 8 (4.8) | 11 (7.1) |
| 39 -54 (20/160 to Worse than 20/80) | 34 (20.2) | 27 (17.5) |
| ≥54 -<74) (20/80 to Worse than 20/32) | 97 (57.7) | 87 (56.5) |
| ≥74 (20/32 or Better) | 29 (17.3) | 28 (18.2) |
| Missing | 0 | 1 (0.6) |
| Central subfield thickness, μm | | |
| No. | 159 | 149 |
| Mean (SD) | 415.9 (143.7) | 410.4 (170.9) |
| Type of lesion, No. (%) | | |
| 100% classic | 2 (1.2) | 1 (0.6) |
| Predominantly classic | 2 (1.2) | 0 |
| Minimally classic | 9 (5.4) | 16 (10.4) |
| Occult with no classic component | 139 (82.7) | 124 (80.5) |
| Cannot grade | 16 (9.5) | 13 (8.4) |
| Presence of massive submacular hemorrhage | | |
| No | 147 (87.5) | 135 (87.7) |
| Yes | 19 (11.3) | 15 (9.7) |
| Cannot grade | 2 (1.2) | 4 (2.6) |
| Presence of serosanguinous hemorrhage | | |
| No | 72 (42.9) | 61 (39.6) |
| Yes | 94 (56.0) | 88 (57.1) |
| Cannot grade | 2 (1.2) | 5 (3.2) |
| Presence of polypoidal lesions | | |
| No | 2 (1.2) | 3 (1.9) |
| Yes | 166 (98.8) | 151 (98.1) |
| Cannot grade | 0 | 0 |
| No. of polypoidal lesions | | |
| 0 | 0 | 0 |
| 1 | 24 (14.3) | 34 (22.1) |
| 2 | 32 (19.0) | 33 (21.4) |
| 3 | 32 (19.0) | 23 (14.9) |
| 4 | 22 (13.1) | 19 (12.3) |
| ≥5 | 56 (33.3) | 42 (27.3) |
| Missing | 2 (1.2) | 3 (1.9) |
| Polyp size, $mm^2$ | | |
| No. | 166 | 151 |
| Mean (SD) | 0.410 (0.426) | 0.379 (0.331) |
| Presence of BVN | | |
| No | 9 (5.4) | 7 (4.5) |
| Yes | 158 (94.0) | 146 (94.8) |
| Cannot grade | 1 (0.6) | 1 (0.6) |
| BVN size, $mm^2$ | | |
| No. | 158 | 146 |
| Mean (SD) | 3.140 (2.765) | 2.614 (2.231) |

Abbreviations: BCVA, best-corrected visual acuity; BVN, branching vascular network.

[a] Percentages are based on total number of participants in the randomized set in the respective treatment group.

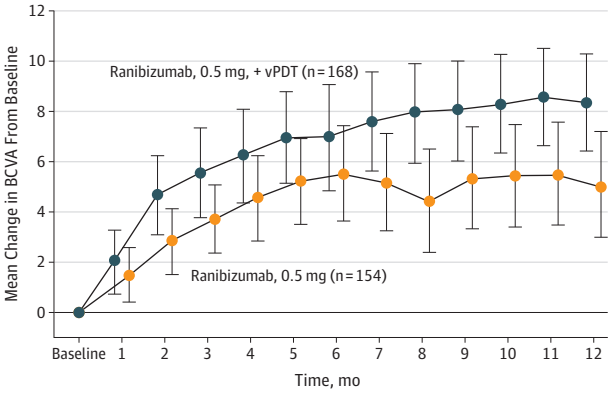
baseline BCVA letter score was similar between the combination (61.1 [approximate Snellen equivalent, 20/63]) and monotherapy groups (61.2 [approximate Snellen equivalent, 20/63]; Table). Most study eyes had occult with no classic component lesion types at baseline (Table). Overall, 294 participants completed the first 12 months of the study (158 in the combination arm and 136 in the monotherapy arm; Figure 1).

## Efficacy

At 12 months, mean improvement from baseline was 8.3 letters with combination therapy vs 5.1 letters with monotherapy (mean difference, 3.2 letters; 95% CI, 0.4-6.1), indicating that combination therapy met the predefined criterion for noninferiority. Combination therapy was statistically superior to ranibizumab monotherapy in improving BCVA from baseline at month 12 (8.3 vs 5.1 letters; $P = .01$, eTable 1 in Supplement 2). Mean change in BCVA from baseline up to month 12 is shown in **Figure 2.** Sensitivity analyses using different modeling methods and approaches for handling missing data and outlier values produced similar results (eTables 2-4 in Supplement 2).

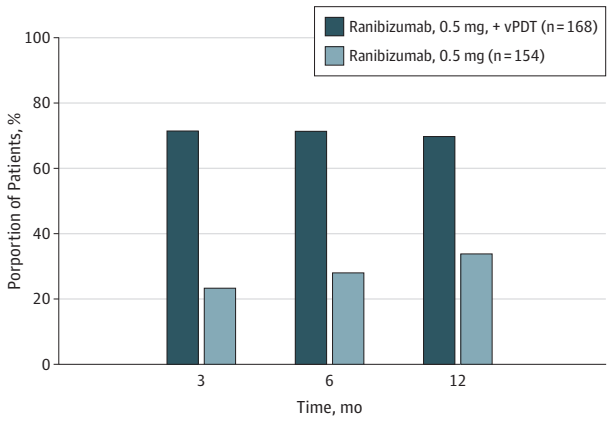
At month 12, 24.5% of participants (n = 38) in the combination arm and 14.0% of participants (n = 19) in the monotherapy arm showed a significant BCVA gain of at least 15 letters ($P = .03$; eFigure 2 in Supplement 2). At month 12, the proportion of participants with BCVA at least 69 letters of the study eye (approximately 20/40 Snellen equivalent) increased from 32.7% at baseline to 69.0% in the combination

Figure 2. Mean Change in Best-Corrected Visual Acuity (BCVA) From Baseline to Month 12 (Full Analysis Set)



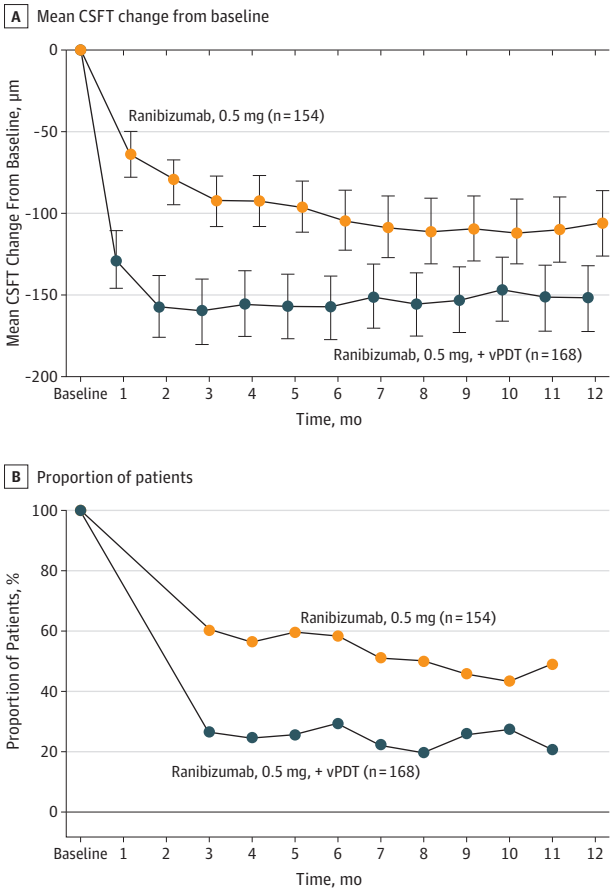

The total counts presented are the counts of patients in the specific treatment group who attended the specific visit. These total counts are used as the denominator for the percentages. Error bars represent 95% CIs. vPDT indicates verteporfin photodynamic therapy.

Figure 3. Proportion of Participants With Complete Polyp Regression by Study Visits up to Month 12 in Full Analysis Set (FAS)




Assessed by Central Reading Center using indocyanine green angiography. Number values indicate the total number of participants in the FAS in the respective treatment group. Percentages are computed by considering the total number of participants in the respective treatment group who attended the specific visit as a denominator. vPDT indicates verteporfin photodynamic therapy.

Figure 4. Mean Central Subfield Thickness (CSFT) Change




Mean CSFT change from baseline to month 12, full analysis set (FAS) (A) and proportion of participants with disease activity by visit (FAS) (B) as assessed by the investigators. Number values indicate the total number of participants in the FAS in the respective treatment group. Percentages are computed by considering the total number of participants in the respective treatment group who attended the specific visit as a denominator. vPDT indicates verteporfin photodynamic therapy.

arm and from 40.8% at baseline to 58.8% in the monotherapy arm (eFigure 6 in Supplement 2).

Combination therapy showed statistically significant superiority to ranibizumab monotherapy in achieving complete polyp regression at month 12 as assessed by ICGA (69.3% vs 34.7%; $P < .001$). The superiority of the combination arm vs the monotherapy arm in achieving complete polyp regression was consistent from months 3 to 12 (**Figure 3**). In the combination therapy group, 51.6% of participants showed absence of leakage on fluorescein angiography at month 12 vs 25% in the monotherapy group (eFigure 3 in Supplement 2).

The mean reduction in CSFT from baseline to month 12 was greater in the combination arm than in the monotherapy arm (least squares mean, −164.9 µm vs −113.4 µm, $P < .001$). Investigator-assessed change in CSFT of the study eye from baseline is illustrated in **Figure 4**A.

The proportion of participants with disease activity from month 3 to month 11 was lower in the combination arm than in the monotherapy arm (month 3, 26.4% vs 60.7% and month 11, 20.5% vs 50.0%; Figure 4B). At month 12, serosanguineous maculopathy was present in 14.8% of participants in the combination group (n = 23) and in 8.8% of participants in the monotherapy group (n = 12), whereas submacular hemorrhage (>4 disc areas) was reported in 1.3% of participants in the combination group (n = 2) and 0.7% of participants in the monotherapy group 1). The anatomic outcomes can be clearly seen in an example case provided (eFigure 4 in Supplement 2).

## Treatment Exposure

The mean (median) number of ranibizumab injections administered up to month 12 was 5.2 (4) for combination therapy and 7.3 (7) for ranibizumab monotherapy, respectively (eTable 5 in

Supplement 2). The difference in the log injection rates between the 2 groups was statistically significant (ratio of injection rates [ranibizumab, 0.5 mg, with vPDT/ranibizumab, 0.5 mg], 0.68; $P < .001$). Approximately 50.6% of participants (n = 87) in the combination arm required 3 or 4 ranibizumab injections vs 26.2% of participants (n = 39) in the monotherapy arm, while 32.2% of participants (n = 48) in the monotherapy arm required 10 to 12 injections over 12 months compared with 8.7% of participants in the combination arm (n = 15) (eFigure 5A in Supplement 2).

The mean (median) number of vPDT treatments in the combination arm was 1.5 (1), and the mean (median) number of sham PDT treatments in the monotherapy arm was 2.3 (2) (eTable 1 in Supplement 2). Overall, 61.0% of the participants in the combination arm needed only the first vPDT at baseline over the 12 months (eFigure 5B in Supplement 2).

### Safety

Vitreous hemorrhage was the only serious ocular AE reported in 1 patient in the combination arm (0.6%) and 3 patients in the monotherapy arm (2.0%) (eTable 6 in Supplement 2). No cases of endophthalmitis or retinal break/detachment were reported in either treatment group. Rates of nonocular serious AEs were comparable between both treatment groups (7.6% in the combination arm vs 7.4% in the monotherapy arm). One patient from the combination group died of chronic obstructive pulmonary disease.

Ocular AEs of the study eye were reported in 26.7% of participants in the combination arm (n = 46) and 25.5% of participants in the monotherapy arm (n = 38) (eTable 7 in Supplement 2). The most common AEs were intraocular pressure increase (5.2% and 4.7%), retinal hemorrhage (3.5% and 0.7%), and conjunctivitis (1.7% and 3.4%) in the combination and monotherapy groups, respectively. Nonocular AEs, regardless of study drug relationship, were reported in 42.4% (n = 73) and 37.6% (n = 56) of participants in the combination and monotherapy groups, respectively.

## Discussion

The 12-month results of EVEREST II demonstrated that ranibizumab in combination with vPDT was not only noninferior but also superior to ranibizumab monotherapy in improving vision. In addition, combination therapy was found to be superior to monotherapy in achieving complete polyp regression. Most patients maintained or reached at least 69 letters with both treatment modalities at month 12 (eFigure 6 in Supplement 2). Despite having high baseline BCVA, participants achieved notable BCVA gains of 8.3 letters and 5.1 letters in the combination and monotherapy groups, respectively. Importantly, over 12 months, the median number of ranibizumab injections was 4 in the combination group compared with 7 in the monotherapy group. This difference in intravitreal injections could be significant in terms of cost-effectiveness in many countries.

Our study should be compared with the few prospective PCV trials in the literature. In the 12-month FUJISAN study, participants receiving combination therapy (either at baseline or deferred) had a VA gain of 8.1 and 8.8 letters, respectively.[21] In contrast, participants with PCV in the DRAGON study showed a BCVA gain of 12.7 and 9.4 letters over 12 months with monthly and PRN ranibizumab monotherapy, respectively.[22] The 12-month VA gains in the PLANET study, which assessed fixed dosing of aflibercept in PCV participants with and without rescue PDT, were reported to be 10.8 and 10.7 letters, respectively.[23] Differences in baseline BCVA across the different studies may account for the differences in BCVA gains because poorer baseline BCVA is an important predictor of superior numerical change in BCVA. The baseline BCVA letter score for the ranibizumab PRN monotherapy arm in EVEREST II (61.2 [approximate Snellen equivalent, 20/63]) was higher than the baseline BCVA in the ranibizumab PRN arm in DRAGON (54.6 [approximate Snellen equivalent, 20/80])[22] and possibly higher than in the aflibercept and sham rescue PDT arm in PLANET (57.7).[23] Importantly, therapeutic outcomes may be underrepresented by simply evaluating VA gains; other factors, such as anatomical responses, polyp regression, and treatment burden, need to be taken into account. In EVEREST, combination therapy was superior to ranibizumab monotherapy in achieving complete polyp regression over 6 months (77.8% vs 28.6%, $P = .002$).[19] Similarly, in EVEREST II, complete polyp regression rates at months 3, 6, and 12 were consistently higher for combination therapy (71.4%, 71.3%, and 69.7%) vs ranibizumab monotherapy (23.3%, 28.0%, and 33.8%). In FUJISAN, the proportion of participants who showed resolution of polypoidal lesions at month 12 was in broad agreement with EVEREST II whether vPDT was given at baseline or deferred (62.1% vs 54.8%, respectively, $P = .53$).[21] Importantly, in contrast to these, complete polyp regression rates at month 12 in PLANET were only 38.9% for the aflibercept and sham PDT arm and 44.8% for the aflibercept and rescue PDT arm.[22] This is substantially lower than combination therapy in EVEREST, EVEREST II, or FUJISAN and, in fact, similar to the 12-month complete polyp regression rates in the ranibizumab monotherapy arm in EVEREST II. Taken together, these findings further strengthen the concept that combination therapy achieves superior BCVA outcomes than anti-vascular endothelial growth factor monotherapy along with concomitant higher polyp closure rates.[24,25] Furthermore, the overall visual and anatomical outcomes of EVEREST II, the largest combination therapy RCT to our knowledge to date, are in concordance with the findings of meta-analyses conducted in 2014 and 2016.[16,24]

In terms of treatment burden, an increasing concern in the anti-vascular endothelial growth factor therapy era, the mean number of ranibizumab injections required by the combination arm was significantly lower than the monotherapy arm. Over 12 months, 50.6% of the participants in the combination arm required 3 to 4 ranibizumab injections, while only 8.7% of participants in this group required 10 to 12 injections. This reduction in injection number was similar to that observed in other studies evaluating combination therapies for the PCV treatment.[21,26] In FUJISAN, initial vPDT therapy led to significantly fewer additional ranibizumab treatments after the 3 loading doses vs deferred vPDT therapy.[22] Combination therapy

may thus help reduce overall treatment burden and ultimately PCV treatment costs.

In EVEREST II, both treatments showed a considerable 12-month reduction in the proportion of participants with serosanguineous maculopathy and massive submacular hemorrhage,[25,26] thus allaying physician fears about posttreatment hemorrhage when using vPDT to treat PCV.[25-31] The safety profiles of both treatment groups were comparable and consistent, with vitreous hemorrhage being the only ocular serious AE reported during 12 months and low rates of retinal hemorrhage in both treatment groups.

Polypoidal choroidal vasculopathy diagnosis has always been challenging owing to its clinical and angiographic resemblance to other retinal pathologies, such as retinal angiomatous proliferation and central serous chorioretinopathy,[18] potentially leading to inappropriate therapy. For example, the efficacy of anti-vascular endothelial growth factor therapy in treating central serous chorioretinopathy is unestablished.[32] Furthermore, in some PCV cases, the polypoidal lesions may be ill-defined or may have extensive bleeding, which renders diagnosis difficult. One of the strengths of EVEREST II was Central Reading Center involvement during screening, using well-defined, stringent criteria modified from EVEREST.[12,15] This ensured that only definite PCV cases were recruited. The EVEREST criteria have also been validated in real-world settings.[3]

### Limitations

The study had a few limitations. The administration of 3 initial monthly injections was presumptive because it was based on nAMD treatment guidelines, which may not apply to combination treatment. Another potential limitation is that only Asian participants with PCV were included, and the results may be ethnospecific. Nevertheless, to our knowledge, no evidence has suggested differential ethnic responses in PCV.

## Conclusions

The 12-month EVEREST II results confirm that combination treatment with ranibizumab and vPDT is effective in improving vision of participants with symptomatic macular PCV. Importantly, combination of ranibizumab with vPDT also helps to achieve complete polyp regression, a key clinical outcome for PCV treatment. These functional and anatomical outcomes were achieved with fewer ranibizumab injections over 12 months, thereby reducing treatment burden.

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**Author Affiliations:** Eye and Retina Surgeons, Camden Medical Centre, Singapore, Singapore (Koh); Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China (Lai); Department of Ophthalmology, Kansai Medical University, Hirakata Hospital, Osaka, Japan (Takahashi); Singapore Eye Research Institute, Singapore National Eye Centre, Duke-NUS Medical School, National University of Singapore, Singapore (Wong); Department of Ophthalmology, Mackay Memorial Hospital, Taipei, Taiwan (Chen); Department of Ophthalmology, Rajavithi Hospital, Bangkok, Thailand (Ruamviboonsuk); Fundus Image Reading Centre, National Healthcare Group Eye Institute, Singapore (Tan, Lim); National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore (Tan, Lim); Novartis Pharma AG, Basel, Switzerland (Feller, Margaron); Department of Ophthalmology, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Korea (Lee).

**Author Contributions:** Drs Koh and Margaron had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design:* Koh, Lai, Chen, Ruamviboonsuk, Tan, Lim, Lee.
*Acquisition, analysis, or interpretation of data:* Lai, Takahashi, Wong, Chen, Ruamviboonsuk, Tan, Feller, Margaron, Lim, Lee.
*Drafting of the manuscript:* Lai, Wong, Ruamviboonsuk.
*Critical revision of the manuscript for important intellectual content:* Koh, Lai, Takahashi, Chen, Ruamviboonsuk, Tan, Feller, Margaron, Lim, Lee.
*Statistical analysis:* Takahashi, Wong, Feller, Margaron.
*Administrative, technical, or material support:* Lai, Takahashi, Tan, Margaron, Lim.
*Supervision:* Koh, Takahashi, Ruamviboonsuk, Margaron, Lim.

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**Group Information:** The EVEREST II study group members are Kanji Takahashi, MD, Kansai Medical University Hospital, Hirakata-city, Osaka, Japan; Kunihiko Shiraki, MD, Osaka City University Hospital, Osaka-city, Osaka, Japan; Yasuo Yanagi, MD, The University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan; Satoshi Kato, MD, PhD, The University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan; Hiroko Terasaki, MD, Nagoya University Hospital, Nagoya-city, Aichi, Japan; Masahito Ohji, MD, Shiga University of Medical Science Hospital, Ohtsu-city, Shiga, Japan; Tetsuju Sekiryu, MD, Fukushima Medical University Hospital, Fukushima-city, Fukushima, Japan; Shoji Kishi, MD, Gunma University Hospital, Maebashi-city, Gunma, Japan; Masahiro Morimoto, MD, Gunma University Hospital, Maebashi-city, Gunma, Japan; Tatsuro Ishibashi, MD, Kyushu University Hospital, Fukuoka city, Fukuoka, Japan; Yuji Oshima, MD, Kyushu University Hospital, Fukuoka city, Fukuoka, Japan; Koh Hei Sonoda, MD, Kyushu University Hospital, Fukuoka city, Fukuoka, Japan; Rvusaburo Mori, MD, Surugadai Nihon University Hospital, Kanda surugadai, Chiyoda, Tokyo, Japan; Ayame Annabelle Okada, MD, Kyorin University Hospital, Shinkawa, Mitaka, Tokyo, Japan; Tomohiro Iida, MD,Tokyo Women's Medical University Hospital, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan; Takayuki Baba, MD, Chiba University Hospital, Inohana Chuo-ku Chiba-shl Chiba, Japan; Fumio Shiraga, MD, Okayama University Hospital, Shikata-cho, Kita-ku, Okayama, Okayama, Japan; Hideyasu Oh, MD, Hyogo Prefectural Amagasaki General Medical Center, Higashinaniwa-cho, Amagasaki-city, Hyogo, Japan; Toshiya Sakurai, MD, Tane Memorial Eye Hospital, Sakaigawa, Nishi-ku, Osaka, Japan; Nagako Kondo, MD, Miyake Eye Hospital, Ozone, Kita- ku, NagOya City, Japan; Shigeru Honda, MD, Kobe University Hospital, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe, Hyogo, Japan; Mineo Kondo, MD,

Mie University Hospital, 2-174, Edobashi, Tsu, Mie, Japan; Masahiro Miura, MD, Tokyo Medical University Ibaraki Medical Center, Inashiki-gun Ibaraki, Japan; Chieko Shiragami, MD, Kagawa University Hospital, Kita-gun, Kagawa Japan; Yasuo Kurimoto, MD, Kobe City Medical Center General Hospital, Kobe-city, Hyogo, Japan; Yuk Yau Timothy LAI, MD, FRCS(Ed), FRCOphtha, FHKAM, Chinese University of Hong Kong, Hong Kong; Lan Y. H. Wong, MMed, FRCS(Ed), FRCOphthaHK, FHKAM, Queen Mary Hospital, Hong Kong; Wonki Lee, MD, The Catholic University of Korea Seoul, St. Mary's Hospital, Seoul, Korea; Hakyoung Kim, MD, PhD, Kangnam Sacred Heart Hospital, Seoul, Korea; Kyu Hyung Park, MD, Seoul National University Bundang Hospital, Bundang Seongnam, Korea; Hyung-Woo Kwak, MD, PhD, Kyung Hee University Hospital, Seoul, Korea; Eung Suk Kim, MD, PhD, Kyung Hee University Hospital, Seoul, Korea; Dongwon Lee, MD, PhD, Kim's Eye Hospital, Seoul, Korea; Taegon Lee, MD, Kim's Eye Hospital, Seoul, Korea; Nikolle Tan, MMed, FRCS(Ed), Tan Tock Seng Hospital, Ophthalmology, Singapore; Rajesh Rajagopalan, MBBS, FRCS(Ed), Tan Tock Seng Hospital Ophthalmology, Singapore; Gemmy Cheung, MBBS, FRCOphtha, Singapore National Eye Centre, Singapore; Caroline Ka Lin Chee, MMed, FRCS(Ed), National University Hospital, Singapore; Shih-Jen Chen, MD, PhD, Taipei Veterans General Hospital, Taipei, Taiwan; Chi-Chun Lai, MD, Chang Gung Memorial Hospital Linkou, Lin-Ko, Taiwan; Lee-Jen Chen, MD, MacKay Memorial Hospital, Taipei, Taiwan; Chung-May Yang, MD, National Taiwan University Hospital, Taipei, Taiwan; San-Ni Chen, MD, Changhua Christian Hospital, Changhua, Taiwan; Shwu-Jiuan Sheu, MD, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; Paisan Ruamviboonsuk, MD, Rajavithi Hospital, Bangkok, Thailand; Prut Hanutasaha, MD, Ramathibodi Hospital, Bangkok, Thailand; Patama Bhurayanontachai, MD, Songklanagarind Hospital, Songkla, Thailand; Nor Fariza Ngah, MBBS, MSc(Ophtha), Hospital Selayang, Batu Caves, Selangor, Malaysia; and Kenneth Choong Sian Fong, FRCOphtha(UK), FRANZCO(Australia), Sunway Medical Centre, Petaling Jaya Selangor Darul Ehsan, Malaysia.

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