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REAL-WORLD EFFECTIVENESS AND SAFETY OF RANIBIZUMAB TREATMENT IN PATIENTS WITH AND WITHOUT POLYPOIDAL CHOROIDAL VASCULOPATHY

Twelve-Month Results From the LUMINOUS Study

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Purpose: To evaluate the real-world effectiveness and safety of intravitreal ranibizumab 0.5 mg in treatment-naive patients with and without polypoidal choroidal vasculopathy (PCV).

Methods: Assessment of neovascular age-related macular degeneration patients with or without PCV after 12 months of ranibizumab treatment during the LUMINOUS study. Outcome measures were visual acuity and central retinal thickness changes from baseline and the rate of ocular adverse events.

Results: At baseline, 572 and 5,644 patients were diagnosed with and without PCV, respectively. The mean visual acuity gain from baseline at Month 12 in the PCV and non-PCV groups was +5.0 and +3.0 letters, respectively; these gains were achieved with a mean of 4.4 and 5.1 ranibizumab injections. Eighty percent of PCV patients and 72.2% of non-PCV patients who had baseline visual acuity ≥73 letters maintained this level of vision at Month 12; 20.6% and 17.9% of patients with baseline visual acuity <73 letters achieved visual acuity ≥73 letters in these groups. Greater reductions in central retinal thickness from baseline were also observed for the PCV group versus the non-PCV group. The rate of serious ocular adverse events was 0.7% (PCV group) and 0.9% (non-PCV group).

Conclusion: LUMINOUS confirms the effectiveness and safety of ranibizumab in treatment-naive patients with PCV.

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Polypoidal choroidal vasculopathy (PCV) is an exudative retinal disorder characterized by the presence of an abnormal branching vascular network with terminal aneurysmal polypoidal lesions located beneath the retinal pigment epithelium.[1,2] Although the natural course of PCV is variable, recurrent serous exudation and hemorrhage from this vascular network can result in the detachment of the retinal pigment epithelium and neurosensory retina, leading to significant and progressive visual impairment.[1,3] Current histopathological evidence suggests that PCV is a variant of Type 1 choroidal neovascularization; therefore, PCV is considered a subtype of neovascular age-related macular degeneration (nAMD).[4–6]

The importance of correctly diagnosing PCV is increasingly recognized because its treatment may vary from other nAMD subtypes.[5] Accurate diagnosis of PCV requires indocyanine green angiography to enable visualization of the characteristic hyperfluorescent polypoidal lesions.[5,7,8] Previous investigations have revealed a greater prevalence of PCV in Asian populations, accounting for between 22% and 55% of nAMD cases, whereas in whites, the proportion of nAMD cases with PCV reportedly ranges between

4% and 25%.[3,9–12] Increased use of indocyanine green angiography, together with advances in other diagnostic techniques, is anticipated to refine estimates of PCV prevalence rates across patient populations.[9]

Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech, Inc, South San Francisco, CA)—an anti–vascular endothelial growth factor (VEGF) therapeutic agent approved for the treatment of nAMD—administered with or without verteporfin photodynamic therapy has demonstrated efficacy in improving visual and anatomical outcomes in patients with PCV in a number of clinical trials[13–17]; however, little has been published on the effectiveness of ranibizumab for treating PCV in real-world settings. To date, real-world ranibizumab studies have largely focused on the treatment of nAMD, without specifically differentiating patients with PCV. Although these studies generally report positive visual outcomes in the first 12 months of therapy, the degree of improvement is often lower than that documented in pivotal ranibizumab nAMD randomized clinical trials (RCTs).[18–21] Attenuated real-world visual gains have been attributed, in part, to suboptimal treatment associated with the burden of intravitreal injections, restricted patient access to treatment in some regions, and greater variation in patient baseline characteristics due to broader study inclusion criteria.[20,22–26]

In the current study, we address the paucity of real-world evidence evaluating the effectiveness of ranibizumab for the treatment of PCV using data from the prospective, real-world LUMINOUS study. Here, we present 12-month visual, anatomical, and safety outcomes of 0.5-mg ranibizumab monotherapy in treatment-naive patients with nAMD subsequently diagnosed with or without PCV. We compare our findings with those from recently published prospective PCV clinical investigations and other real-world studies of ranibizumab for the treatment of nAMD.

Methods

Ethics Statement

The Declaration of Helsinki and Guideline for Good Clinical Practice from the International Conference on Harmonization were adhered to throughout this study.[27,28] Approval was obtained from the ethics committee or institutional review board at each participating center, and each patient provided written informed consent to participate in the study.

Study Design and Patient Enrollment

LUMINOUS (ClinicalTrials.gov identifier NCT01318941) was a global, 5-year, prospective, observational, noninterventional, open-label, multicenter study designed to evaluate the long-term effectiveness, safety, and treatment patterns associated with intravitreal ranibizumab 0.5 mg administered in real-world clinical practice for all approved indications (nAMD including patients with PCV, diabetic macular edema, macular edema due to branch or retinal vein occlusion, and choroidal neovascularization secondary to pathologic myopia) according to the local product label. The study was conducted from March 2011 to April 2016 across 488 sites in 42 countries.

For the LUMINOUS study as a whole, consenting adult patients (18 years or older) either who were treatment-naive (i.e., patients who had not been pretreated with any intravitreal medication in the primary treated eye) or who had been previously treated with ranibizumab or other ocular therapies in the primary treated eye were eligible for enrollment. Patients were excluded if they were simultaneously participating in a study that included administration of any investigational drug or procedure or if they had received systemic or ocular treatment with any anti-VEGF therapy other than ranibizumab, 90 or 30 days before enrollment, respectively. Patients with known

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None of the authors has any conflicting interests to disclose.

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The LUMINOUS study steering committee members are listed in Supplemental Digital Content 1, Appendix 1, http://links.lww.com/IAE/B53.

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hypersensitivity to ranibizumab, with active or suspected ocular or periocular infections or with active severe intraocular inflammation, were also excluded from the study.

Study Population

In the current study, the cohort of treatment-naive patients with nAMD who were recruited in LUMINOUS and subsequently screened for symptomatic macular PCV in their primary treated eye comprised the patient population considered for analysis. For diagnosis of PCV, it was recommended that investigators use indocyanine green angiography to identify the presence of active macular polypoidal lesions. It was also recommended that investigators perform color fundus photography, fluorescein angiography, or optical coherence tomography to identify the presence of serosanguineous maculopathy in patients. Patients who presented with or without PCV lesions comprised the global PCV and non-PCV groups analyzed here, respectively.

Treatment Protocol

No treatment protocols were specified in this study. Follow-up visits took place at a frequency defined by the investigator; however, it was recommended to collect data at every patient visit or at a minimum of every 3 months. Physicians were encouraged to follow-up with patients who had not been assessed in the clinic for at least 6 months since their last visit to collect and register data. Patients not assessed at least once per year were discontinued from the study.

The first eye treated during the study was considered as the primary treated eye. If both eyes were treated on the same date, the eye with the earliest diagnosis date was considered the primary treated eye. If both eyes had the same diagnosis date, one eye was chosen randomly as the primary treated eye. These criteria ensured that only one eye per patient was included in any analysis.

Data Collection

All data were collected anonymously and entered directly into an electronic data collection system (maintained by IQVIA on behalf of Novartis) through electronic case report forms by the treating physician(s) at each participating center. To ensure the accuracy and completeness of the data collected, all electronic case report forms, together with site adherence to the guidelines for good pharmacoepidemiology practices of the International Society for Pharmacoepidemiology,[29] were regularly reviewed by IQVIA staff. Additional centralized quality control audits were made before the database lock.

Study Measurements

The following patient data were collected at baseline, where baseline was defined as the first on-study ranibizumab injection: demographic data (age, gender, and ethnicity, where permitted under local regulations), the primary indication for the initiation of ranibizumab treatment including the date of diagnosis in each eye, ocular and nonocular medical histories, patient comorbidities, and relevant previous and concomitant medications.

Visual acuity (preferably best-corrected visual acuity) was measured according to the method used by the treating physician. To ensure consistency, it was recommended that the same visual acuity assessment method be used throughout the study wherever possible. Baseline visual acuity was recorded in the primary treated eye and was captured in the electronic case report form, which allowed the use of Early Treatment Diabetic Retinopathy Study (ETDRS) letters or Snellen charts. If a Snellen fraction or decimal score was entered, it was converted into an approximate ETDRS equivalent letter score for the purpose of statistical analysis. Therefore, it was recommended that ETDRS-like sight charts be used if available. Baseline central retinal thickness (CRT; measured with optical coherence tomography) was recorded optionally as per the treating center's routine care practice. All visual acuity measurements, ocular adverse events (AEs), and nonocular AEs were recorded at each patient follow-up visit. Information on ranibizumab administration, reasons for dosing, and treatment status during the study were also collected. Follow-up CRT measurements were recorded during patient visits as per the discretion of the treating physician.

Study Objectives and Outcomes

The primary objective of the current study was to assess the effectiveness and safety of intravitreal ranibizumab 0.5 mg in the global PCV and non-PCV patient groups. The primary study outcome used to assess effectiveness was the mean change in visual acuity from baseline at Month 12. Secondary effectiveness outcomes were the mean change in CRT from baseline at Month 12, the mean number of ranibizumab injections received, and the mean number of patient visits in the first 12 months of treatment. Safety outcomes were assessed by the type, frequency, severity, and relationship of all systemic and ocular AEs or serious AEs (SAEs) reported for the primary

eye. Safety data were collected for each patient until their last recorded follow-up visit and are reported here.

Data Analysis

All effectiveness and safety data were summarized descriptively and are presented as mean (SD) or number (percentage). Hypothesis testing was not predefined for LUMINOUS, and hence, no statistical tests were performed in the current study.

The assessment of effectiveness was based on those patients who had both baseline and 12-month follow-up data and who had remained in the LUMINOUS study for a period of at least 365 days. To assess visual acuity maintenance, gain, or loss, yearly summaries were provided for the proportion of patients with an absolute visual acuity score of ≥73 letters; proportions of patients with gains in visual acuity of ≥1 letter, ≥5 letters, ≥10 letters, and ≥15 letters compared with baseline; and proportions of patients with a loss in visual acuity <10 letters and <30 letters compared with baseline. The analysis set for safety comprised all patients who were treated with at least one dose of ranibizumab and had at least one safety assessment after treatment. For AEs or SAEs with multiple occurrences, the first occurrence was analyzed.

As the prevalence of PCV is higher in Asian versus non-Asian patient populations,[3,10,12] the mean changes in visual acuity and CRT from baseline at Month 12 stratified by patient population (i.e., Asian vs. non-Asian) and by the presence of PCV were also evaluated. In LUMINOUS, the demarcation of Asian and non-Asian patients was based on the geographical location of the site where a patient was recruited and not ethnicity.

Results

Study Enrollment, Patient Demographics, and Baseline Ocular Characteristics

The LUMINOUS study recruited 30,153 patients worldwide. Of these, 6,241 were treatment-naive patients with nAMD. The participating countries and associated patient recruitment figures are presented in **Supplementary Digital Content 1**, (see, **Appendix 2**, http://links.lww.com/IAE/B53). Data regarding time since diagnosis were available for all treatment-naive patients, and the mean (SD) value was 121.0 (417.06) days. During the first 3 months, patients received a total of 14,709 injections, with a mean (SD) of 2.4 (0.86) injections per patient.

Data regarding PCV status at baseline were available for 6,216 (99.6%) treatment-naive patients with nAMD from 38 countries. Of these, PCV was present in a total of 572 (9.2%) patients and absent in the remaining 5,644 (90.8%) patients; these patients comprised the global PCV and non-PCV groups analyzed here, respectively (see **Supplemental Digital Content 2**, http://links.lww.com/IAE/B54).

In the PCV group, Asians (73.6%, n = 421) had the greatest representation followed by whites (24.8%, n = 142), with the converse observed for the global non-PCV patient group (whites: 70.8%, n = 3,995; Asians: 24.8%, n = 1,398). Country-level PCV prevalence—calculated here as the proportion of patients from each country who presented with PCV at baseline—was highest in Asia, most notably Malaysia (58.5%, n = 24), Singapore (40.9%, n = 9), Japan (33.0%, n = 260), and South Korea (31.6%, n = 48); PCV also presented in all four patients recruited from Hong Kong. Polypoidal choroidal vasculopathy was detected in patients from 20 countries outside of Asia, ranging in prevalence from 0.4% (Canada, n = 2) to 20.0% (Egypt, n = 1) (see **Supplemental Digital Content 2**, http://links.lww.com/IAE/B54).

Baseline demographic and ocular characteristics for the PCV and non-PCV groups are summarized in Table 1. The PCV group had a lower mean (SD) age (72.8 [9.7] years) and showed a male preponderance (60.7%) compared with the non-PCV group (75.2 [10.2] years; 43.5% males). The mean (SD) baseline visual acuity and CRT values were available for a total of 539 and 431 patients in the PCV group and 5,235 and 4,147 patients in the non-PCV group, respectively. The mean (SD) baseline visual acuity and CRT was higher in the PCV group (visual acuity: 53.8 [23.6] letters; CRT: 374.4 [156.0] μm) compared with the non-PCV group (visual acuity: 49.2 [21.7] letters; CRT: 364.8 [141.2] μm).

Patient Disposition and Visual Acuity Outcomes at Month 12

Of the 6,241 treatment-naive patients with nAMD recruited to LUMINOUS, 1,466 patients discontinued during the first year of the study, the most frequent reasons being loss to follow-up (n = 715; 11.5%) and switch to another anti-VEGF (n = 369; 5.9%). Of the 4,768 patients who were ongoing in the study at Month 12, baseline and visual acuity follow-up data were available for a total of 274 patients with PCV and 3,093 patients without PCV (Figure 1). The global mean improvement in visual acuity from baseline was greater for the PCV group (+5.0 [16.9] letters from a mean baseline of 55.4 [23.3] letters) compared

Table 1. Baseline Demographic and Ocular Characteristics for Treatment-Naive Patients With nAMD Presenting With or Without PCV at Baseline

Characteristics	PCV (N = 572)*	Non-PCV† (N = 5,644)*
Mean (SD) age, years	72.8 (9.7)	75.2 (10.2)
Gender (n, %)‡		
Male	347 (60.7)	2,455 (43.5)
Female	225 (39.3)	3,189 (56.5)
Ethnicity (n, %)		
White	142 (24.8)	3,995 (70.8)
Black	0 (0)	8 (0.1)
Asian	421 (73.6)	1,398 (24.8)
Native American	0 (0)	11 (0.2)
Pacific Islander	1 (0.2)	4 (0.1)
Other	7 (1.2)	185 (3.3)
Missing	1 (0.2)	43 (0.8)
Ocular characteristics		
Visual acuity		
n‡	539	5,235
Mean (SD), ETDRS letters	53.8 (23.6)	49.2 (21.7)
CRT		
n‡	431	4,147
Mean (SD) (μm)	374.4 (156.0)	364.8 (141.2)

*N, total number of patients at enrollment.
†Non-Asian refers to whites, blacks, Native Americans, and Pacific Islanders. Patients with missing ethnicity have been excluded from non-Asian category but included in the global summary.
‡n, number of patients with evaluable data at baseline.

with the non-PCV group (+3.0 [16.5] letters from a mean baseline of 51.6 [20.8] letters).

Greater mean gains in visual acuity from baseline were also observed in the PCV versus the non-PCV groups in both the Asian and non-Asian patient populations. The non-Asian patients showed mean gains from baseline of +2.7 (13.9) letters versus +2.6 (16.0) letters in the PCV and non-PCV groups, respectively. The improvements were more pronounced in the Asian population, as was the difference between the two groups: +6.4 (18.3) letters versus +5.1 (18.9) letters in the PCV and non-PCV groups, respectively (Figure 2 and see **Supplemental Digital Content 3**, http://links.lww.com/IAE/B55).

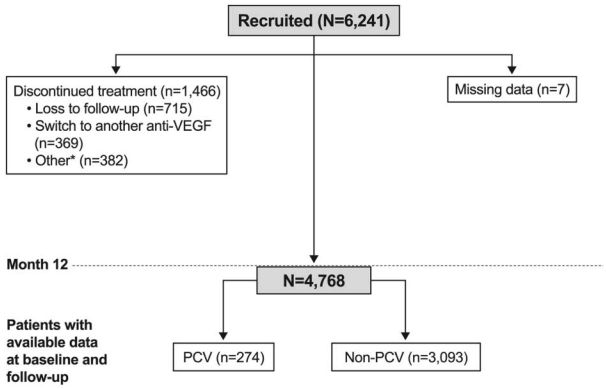

Fig. 1. Patient disposition in the LUMINOUS study. *AEs, unsatisfactory therapeutic effect, consent withdrawal, no longer requiring study drug, administrative problems, and death.

The Relationship Between Baseline Visual Acuity and 12-Month Visual Acuity Outcomes

Vision was either improved or maintained at Month 12 for each baseline visual acuity stratum in the PCV and non-PCV groups, with greater mean visual acuity gains observed for the lower baseline visual acuity strata. In the PCV group, the mean (SD) visual acuity changes for baseline visual acuity strata of <23 (n = 30), 23 to <39 (n = 47), 39 to <60 (n = 55), 60 to <74 (n = 67), and ≥ 74 letters (n = 75) were +20.1 (23.1), +9.5 (20.3), +6.4 (15.0), +0.3 (14.6), and -0.5 (8.7) letters, respectively. The corresponding mean visual acuity changes in the non-PCV group were +11.9 (SD: 20.3; n = 352), +6.5 (SD: 17.6; n = 511), +3.3 (SD: 16.5; n = 869), +0.3 (SD: 13.8; n = 923), and -3.4 (SD: 12.3; n = 438) letters (Figure 3).

Maintenance, Gain, and Loss of Visual Acuity at Month 12

In total, 75 and 450 global patients with and without PCV had baseline visual acuity ≥ 73 letters, and of these, 60 (80.0%) and 327 (72.2%) patients maintained this level of vision at Month 12, respectively. Furthermore, 20.6% (n = 41) and 17.9% (n = 473) of the 199 and 2,643 patients with and without PCV who had baseline visual acuity <73 letters achieved visual acuity ≥ 73 letters at Month 12. The proportions of patients with and without PCV who maintained or achieved visual acuity ≥ 73 letters at

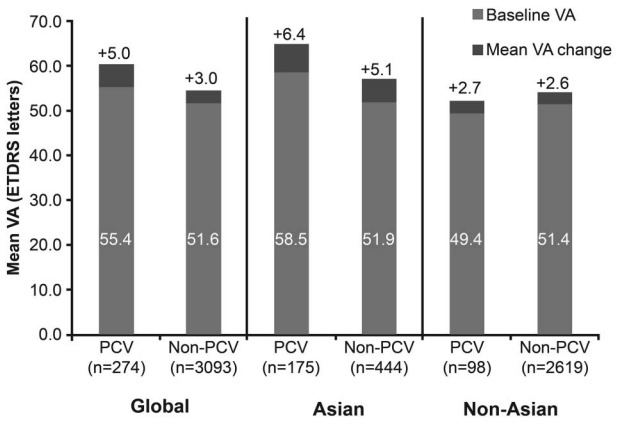

Fig. 2. Mean changes in visual acuity from baseline to Month 12 for the global, Asian, and non-Asian PCV and non-PCV groups. Non-Asian refers to whites, blacks, Native Americans, and Pacific Islanders.

Month 12 in Asian and non-Asian patient populations were broadly comparable with those reported for the global groups (see **Supplemental Digital Content 4**, http://links.lww.com/IAE/B56).

The proportions of global patients with gains of ≥5 letters, ≥10 letters, and ≥15 letters at Month 12 were 47.8% (n = 131), 32.5% (n = 89), and 25.2% (n = 69) in the PCV group, with corresponding proportions of 45.1% (n = 1,395), 29.4% (n = 910), and 20.7% (n = 639) in the non-PCV group, respectively. Loss of ≥5 letters, ≥10 letters, and ≥15 letters at Month 12 was observed in 21.9% (n = 60), 14.2% (n = 39), and 9.9% (n = 27) of patients in the PCV group, and 25.8% (n = 798), 16.4% (n = 506), and 11.6% (n = 360) of patients in the non-PCV group. The proportions of patients gaining or losing ≥5 letters, ≥10 letters, and ≥15 letters in the PCV and non-PCV groups in the Asian and non-Asian patient populations were comparable with those observed globally (see **Supplemental Digital Content 5**, http://links.lww.com/IAE/B57).

Treatment Exposure

The frequency distribution of ranibizumab injections for patients with baseline and 12-month visual acuity follow-up data in the global PCV and non-PCV groups is shown in **Supplemental Digital Content 6**, http://links.lww.com/IAE/B58. The mean (SD) number of injections received in the first 12 months of treatment by the PCV group (4.4 [2.3]) was lower than that received by the non-PCV group (5.1 [2.7]), with a comparable mean number of visits in both groups (PCV: 9.1 [3.5]; non-PCV: 8.8 [3.3]) (see **Supplemental Digital Content 3**, http://links.lww.com/IAE/B55). Further inspection of the injection frequency distributions showed that 85.4% and 71.7% of patients in the PCV and non-PCV group, respectively, received <7 ranibizumab injections in the first 12 months of treatment.

A different trend with regard to injection frequency was observed in the Asian population, with the PCV group receiving a mean (SD) of 4.2 (1.9) injections in the first 12 months of treatment, whereas the non-PCV group received 3.9 (2.3) injections over the same

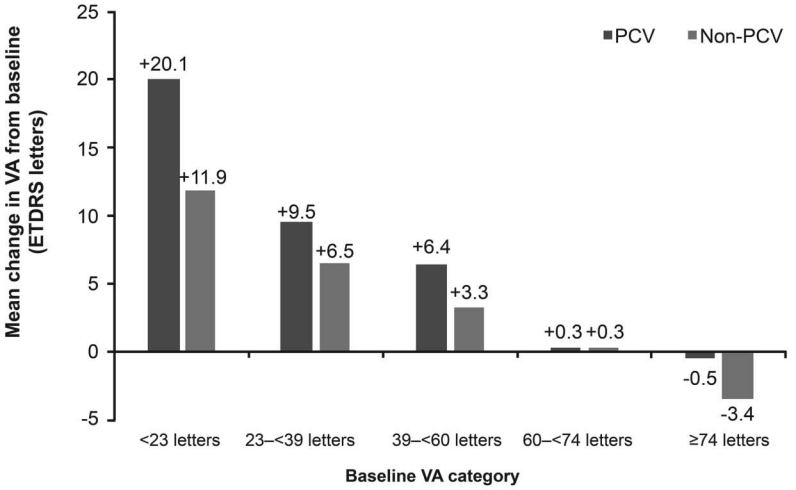

Fig. 3. Mean changes in visual acuity from baseline to Month 12 stratified by baseline visual acuity for the global PCV and non-PCV groups. Non-Asian refers to whites, blacks, Native Americans, and Pacific Islanders.

Baseline VA category	<23 letters		23–<39 letters		39–<60 letters		60–<74 letters		≥74 letters	
Patient group	PCV	Non-PCV	PCV	Non-PCV	PCV	Non-PCV	PCV	Non-PCV	PCV	Non-PCV
Mean (SD) baseline VA	10.4 (7.5)	10.7 (7.8)	33.0 (4.0)	33.1 (3.7)	50.4 (4.8)	50.6 (5.8)	66.9 (3.6)	65.6 (3.9)	80.6 (5.2)	78.2 (3.9)
Number of patients	30	352	47	511	55	869	67	923	75	438

period. The mean (SD) number of visits was 9.0 (3.8) and 8.3 (3.8) in the PCV and non-PCV groups of the Asian population, respectively (see **Supplemental Digital Content 3**, http://links.lww.com/IAE/B55).

The Relationship Between Treatment Frequency and Visual Acuity Outcomes

Increased injection frequency was generally associated with higher 12-month visual acuity gains in both global patient groups. Patients with PCV who received <3 injections (n = 54) did not show any mean (SD) visual acuity change from baseline at Month 12 (+0.0 [17.4] letters), whereas those receiving 3 to 6 (n = 180) and >6 injections (n = 40) showed mean gains of +6.6 (17.4) and +4.9 (12.4) letters from baseline, respectively. Similarly, in the non-PCV group, patients receiving <3 injections (n = 480), 3 to 6 injections (n = 1738), and >6 injections (n = 875) showed mean visual acuity gains from baseline of +1.7 (14.6), +3.0 (16.5), and +3.7 (17.4) letters, respectively (Figure 4).

Central Retinal Thickness Outcomes

Globally, a total of 198 patients with PCV and 2,103 patients without PCV had evaluable CRT data at baseline and Month 12. Greater mean (SD) reductions from baseline were observed at Month 12 for the PCV group (−91.3 [157.8] μm) relative to the non-PCV group (−71.9 [133.0] μm). The mean reductions in CRT from baseline were also greater for the PCV groups compared with the non-PCV groups in the Asian and non-Asian patient populations (Figure 5 and see **Supplemental Digital Content 7**, http://links.lww.com/IAE/B59).

Safety Outcomes

Cumulative 5-year ocular and nonocular AE data (see **Supplemental Digital Content 8**, http://links.lww.com/IAE/B60) and ocular and nonocular SAE data (Table 2) were assessed for both the global PCV and non-PCV groups. In total, ocular AEs were reported in 6.5% (n = 37) of patients with PCV, the most frequent of which were ocular hypertension (0.9%; n = 5) and cataract (0.7%; n = 4). In the non-PCV group, ocular AEs were reported in 8.4% (n = 471) of patients; cataract (1.9%; n = 109), increased intraocular pressure (0.6%; n = 31), and conjunctival hemorrhage (0.5%; n = 30) were the most common of these. The rates of retinal and vitreous hemorrhage for the PCV group were 0.4% (n = 2) and 0.7% (n = 4), respectively, and were marginally higher than those observed for the non-PCV group (retinal hemorrhage: 0.3%, n = 17; vitreous hemorrhage: 0.1%, n = 3). The overall rate of ocular SAEs was 0.7% (n = 4) for the PCV group and 0.9% (n = 52) for the non-PCV group.

The incidence of nonocular AEs and SAEs was 5.9% (n = 34) and 3.9% (n = 22) for the PCV group and 13.4% (n = 756) and 7.7% (n = 436) for the non-PCV group. Death was reported in 0.5% (n = 3) of

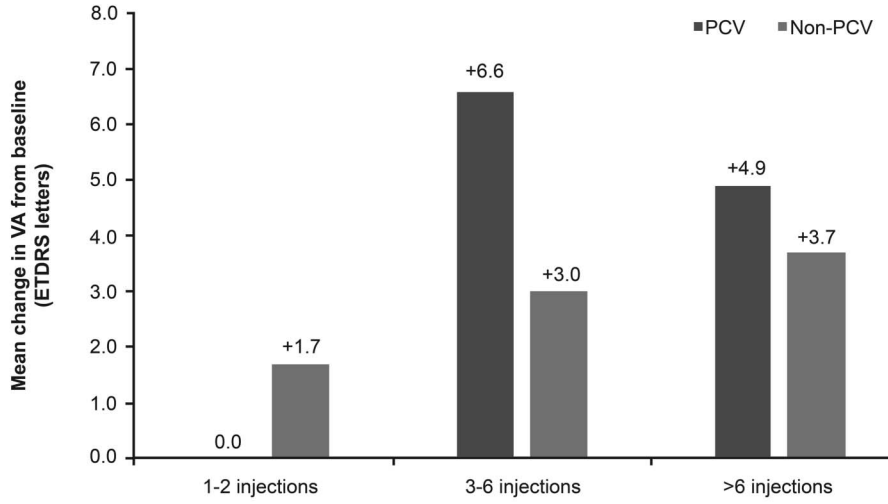

Fig. 4. Mean change in visual acuity from baseline at Month 12 stratified by injection frequency for the global PCV and non-PCV groups. Non-Asian refers to whites, blacks, Native Americans, and Pacific Islanders. Patients with missing ethnicity have been excluded from non-Asian category but included in the global summary.

Injection stratum	1-2 injections		3-6 injections		>6 injections	
Patient group	PCV	Non-PCV	PCV	Non-PCV	PCV	Non-PCV
Mean (SD) baseline VA	50.2 (26.1)	44.9 (24.2)	56.7 (22.6)	51.9 (20.0)	56.1 (22.4)	54.5 (1 9.4)
Number of patients	54	480	180	1,738	40	875

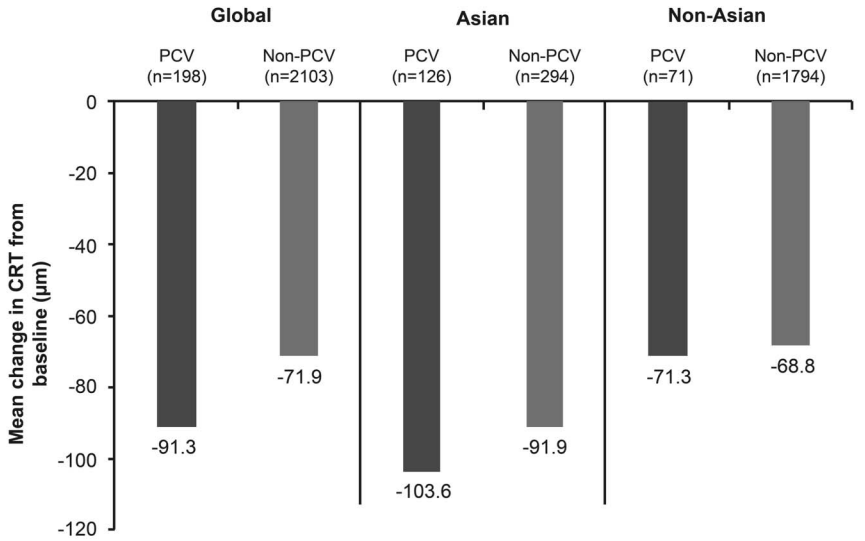

Fig. 5. Mean changes in CRT from baseline to Month 12 for the global, Asian, and non-Asian PCV and non-PCV groups. Non-Asian refers to whites, blacks, Native Americans, and Pacific Islanders. Patients with missing ethnicity have been excluded from non-Asian category but included in the global summary.

	Global		Asian		Non-Asian	
Patient group	PCV	Non-PCV	PCV	Non-PCV	PCV	Non-PCV
Mean baseline CRT (SD), µm	387.7 (170.2)	359.5 (134.5)	370.6 (177.8)	375.5 (159.9)	419.5 (153.0)	357.0 (130.1)

patients in the PCV group and 0.9% (n = 49) in the non-PCV group, none of which were suspected by the investigator to be related to the study treatment. No new safety signals were identified in the PCV and non-PCV groups analyzed here.

Discussion

To the best of our knowledge, this analysis of data from the LUMINOUS study represents the first large-scale, global evaluation of the real-world effectiveness and safety of intravitreal ranibizumab 0.5 mg in treatment-naive patients with and without PCV during the first year of therapy. Our results demonstrate that ranibizumab is an effective, well-tolerated treatment for patients with PCV and reinforces the association between baseline visual acuity and the frequency of treatment with functional outcomes.

The global prevalence of PCV was estimated in the current study at 9.2%. In countries where PCV was detected, prevalence ranged from 5.7% to 58.5% in Asia and from 0.4% to 20.0% elsewhere. These prevalence estimates are consistent with previous studies, which show that PCV occurs in approximately 22% to 55% of Asian patients and 4% to 25% of white patients with nAMD.[3,9–12] It is important to note that these wide prevalence ranges may be due, in part, to the inconsistent methodologies used to evaluate the presence of PCV and the small number of patients recruited from some countries to the LUMINOUS study.[12]

Robust 12-month visual improvements in patients with PCV have been reported for the ranibizumab monotherapy arms of a number of recent prospective RCTs.[13,15–17,30] Similarly, in LUMINOUS, ranibizumab monotherapy resulted in mean visual acuity gains from baseline of +5.0 letters in the global PCV group versus +3.0 letters for the global non-PCV group, with greater reductions in CRT from baseline observed in the PCV group (-91.3 μm vs. -71.9 μm) at Month 12. Greater improvements in visual acuity and CRT outcomes were also noted in the PCV group relative to the non-PCV group in both the Asian and non-Asian patient populations. We detected visual acuity gains $\geq$5 letters from baseline in 47.8% of patients with PCV, whereas 80.0% of patients who had baseline visual acuity $\geq$73 letters maintained this level of vision in the first 12 months of ranibizumab treatment. Collectively, these outcomes from LUMINOUS and recently completed RCTs support ranibizumab monotherapy as an effective first-line treatment for PCV.

Our analysis underscores the importance of baseline vision for final visual outcomes. For both the global PCV and non-PCV groups, vision was either improved or maintained in each baseline visual acuity stratum, with the mean change in visual acuity at Month 12 inversely related to baseline visual acuity. However, despite the larger gains in the lower baseline visual acuity strata, the final 12-month visual acuity

Table 2. Proportion of Patients With Ocular and Nonocular SAEs for the PCV and Non-PCV Groups

Preferred Term, n* (%)	PCV (N = 572)†‡	Non-PCV§ (N = 5,644)†¶
Ocular SAEs**, total	4 (0.70)	52 (0.92)
Cataract	1 (0.18)	5 (0.09)
Glaucoma	1 (0.18)	1 (0.02)
Retinal hemorrhage	1 (0.18)	5 (0.09)
Subretinal hematoma	1 (0.18)	0 (0.00)
Endophthalmitis	0 (0.00)	11 (0.20)
Macular hole	0 (0.00)	5 (0.09)
Retinal pigment epithelial tear	0 (0.00)	5 (0.09)
Preferred Term, n (%)	**PCV (N = 572)†††**	**Non-PCV (N = 5,644)†‡‡**
Nonocular SAEs**, total	22 (3.85)	436 (7.73)
Cerebrovascular accident	3 (0.52)	24 (0.43)
Death	3 (0.52)	49 (0.87)
Angina pectoris	1 (0.18)	11 (0.20)
Atrial fibrillation	1 (0.18)	15 (0.27)
Fall	1 (0.18)	14 (0.25)
Lung neoplasm malignant	1 (0.18)	10 (0.18)
Myocardial infarction	1 (0.18)	16 (0.28)
Pneumonia	1 (0.18)	28 (0.50)
Cardiac failure	0 (0.00)	10 (0.18)
Dyspnea	0 (0.00)	10 (0.18)
Transient ischemic attack	0 (0.00)	10 (0.18)

Data are shown for the primary treated eye. Data collected until the last recorded follow-up date were used to perform the analyses (i.e., data for 5-year duration of the LUMINOUS study).

*n, number of patients.

†N, total number of patients at enrollment.

‡All ocular SAEs are shown for the PCV group. The corresponding values are shown for the non-PCV group.

§Non-Asian refers to whites, blacks, Native Americans, and Pacific Islanders. Patients with missing ethnicity have been excluded from the non-Asian category but included in the global summary.

¶For the non-PCV group, ocular SAEs numbering ≥5 are shown with the corresponding value shown for the PCV group, where applicable.

**An SAE was determined based on its severity according to the treating physician.

††A threshold of ≥2 nonocular SAEs was applied to the PCV group with the corresponding value shown for the non-PCV group, where applicable.

‡‡A threshold of ≥10 nonocular SAEs was applied to the non-PCV group with the corresponding value shown for the PCV group, where applicable.

outcomes were superior for the higher baseline visual acuity stratum. This is consistent with previous real-world ranibizumab studies describing a "ceiling effect" in visual acuity gains, in which the potential for visual improvement in patients with baseline vision ≥70 letters is generally limited.[31–33] These results also show that early diagnosis and treatment of PCV are key to maintaining good baseline vision at Month 12 and achieving optimal visual outcomes in real-world clinical practice.

In LUMINOUS, the 12-month mean visual acuity improvements of +5.0 and +3.0 letters for the PCV and non-PCV groups (achieved with a mean of 4.4 and 5.1 ranibizumab injections, respectively) are comparable with those reported in previous real-world studies of ranibizumab for nAMD.[22,33–35] However, the injection frequencies reported in the current study are markedly lower than those expected in the first year of therapy under strict monthly fixed-dosing (i.e., 12 injections) or treat-and-extend (i.e., 7 injections) regimens.[36] Here, a total of 85.4% of patients with PCV and 71.7% of patients without PCV received fewer than 7 ranibizumab injections, whereas 0.0% of patients with PCV and 1.8% of patients without PCV received ≥12 injections. These results suggest that in real-world settings, patients with nAMD, including those with PCV, are susceptible to undertreatment of disease activity, which may lead to suboptimal clinical outcomes.[26]

The potential impact of undertreatment on visual outcomes in patients with PCV is most noticeable when the visual outcomes from the current study are compared with those from recent PCV clinical studies. For example, in the 12-month FUJISAN study, patients receiving ranibizumab monotherapy with deferred verteporfin photodynamic therapy had best-corrected visual acuity gains from baseline of +8.8 letters (mean of approximately 6.8 injections), whereas in the DRAGON study, mean best-corrected visual acuity improvements of +12.7 and +9.4 letters were

observed with monthly (mean of 11.2 injections) and pro re nata (mean of 8.4 injections) ranibizumab monotherapy, respectively.[16,30] We posit that the attenuated visual outcomes observed in the LUMINOUS PCV group relative to those from recent RCTs may be, in part, associated with low injection frequency. Previous real-world studies of nAMD have demonstrated a positive relationship between ranibizumab injection frequency and visual acuity outcomes,[25,37] and consistent with this, our analysis shows that amelioration of vision occurred in patients with PCV who received, on average, >3 injections. Our findings therefore support the need for sustained ranibizumab treatment to improve or preserve vision in patients with PCV in routine clinical practice.

The low injection frequency observed in the current study may be attributable to: 1) differences in the underlying health care systems of the countries included in the LUMINOUS study, which may impact treatment availability and treatment reimbursement; 2) reduced patient compliance and follow-up, possibly associated with the burden of frequent intravitreal injections and clinic visits; and 3) the discretion of physicians to retreat at subsequent visits.[22,26,38,39] It is also noteworthy that outcomes from LUMINOUS may be influenced by patient heterogeneity at baseline because of wider inclusion criteria, which are typically controlled for in RCTs.[22,23]

Across all treatment-naive patients with and without PCV, the frequency of ocular and nonocular SAEs and AEs was low. These groups demonstrated similar safety profiles to those reported in previous prospective ranibizumab RCTs, and no new safety signals were observed here, despite a patient population with a broader range of disease characteristics and comorbidity profiles.[13,16,18,21,30,36,39] Furthermore, the relatively low proportion of patients in the global PCV and non-PCV groups losing ≥5 letters in the first year of treatment reemphasizes the importance of initiating ranibizumab therapy in patients as early as possible to optimize visual outcomes.

This study has several strengths and limitations. Among this study's strengths are its large sample size, prospective design, global evaluation of ranibizumab's effectiveness in a heterogeneous patient population, and the potential for long-term patient follow-up.

This study also has a number of limitations. First, the generalizability of the study outcomes is limited by the restriction of patient recruitment to sites with the ability to capture data for research purposes. Across these sites, the potentially different diagnostic techniques used by the study investigators may have led to variability in the diagnosis of PCV. Furthermore, owing to the lack of a comparator arm, the effect of treatment versus nontreatment cannot be measured. Second, the 12-month outcomes presented here may be subject to a patient selection bias, as treatment discontinuation (23.5% of patients during the first year of the study, including 5.9% who switched to another anti-VEGF agent) resulted in a loss of patient follow-up data. Also, 12-month data may not have been available for all patients, as the clinic visits scheduled by the investigator fell outside the 12-month evaluation window. Third, as with all real-world studies, the wide inclusion criteria of LUMINOUS did not impose restrictions on baseline visual acuity, baseline lesion size and baseline lesion number, baseline disease activity, and the recruitment of poor responders; these baseline characteristics may have influenced the final study outcomes. Finally, the demarcation of Asian and non-Asian patients—based on the geographical location of the site where a patient was recruited and not ethnicity—may have biased the country-level estimates of PCV prevalence.

In summary, the findings of LUMINOUS demonstrate that ranibizumab is an effective first-line anti-VEGF therapy for the treatment of patients with nAMD, regardless of PCV status, in routine clinical settings. Our analysis supports the effectiveness and safety of ranibizumab under the real-world conditions of patient and clinical heterogeneity and variable treatment regimens. The results from LUMINOUS also reiterate the importance of early, adequate, and sustained ranibizumab treatment to optimize patient outcomes. Further follow-up analyses of the LUMINOUS PCV cohort are expected to provide clinical evidence of the long-term effectiveness of ranibizumab treatment for this nAMD variant in real-world clinical practice.

Key words: visual acuity, central retinal thickness, effectiveness, LUMINOUS, neovascular age-related macular degeneration, polypoidal choroidal vasculopathy, ranibizumab, real-world outcomes, safety, vascular endothelial growth factor.

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