

Real-world effectiveness, treatment pattern, and safety of ranibizumab in Korean patients with neovascular age-related macular degeneration: Subgroup analyses from the LUMINOUS study

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Abstract

Background To evaluate the real-world effectiveness, treatment patterns, and safety of ranibizumab in Korean patients with neovascular age-related macular degeneration (nAMD). **Methods** LUMINOUS™ is a 5-year, global, prospective, observational, open-label study. Adults aged ≥ 18 years who were either treatment-naïve or prior-treated were enrolled and treated with ranibizumab 0.5 mg per the local label. Outcome measures included mean (\pm standard deviation) changes from baseline in visual acuity (VA) and central retinal thickness (CRT), and rate of ocular and non-ocular adverse events (AEs). **Results** Overall, 367 Korean patients with nAMD (152 treatment-naïve and 215 prior-treated) were enrolled. The mean VA changes from baseline at 1-year were $+10.1$ (± 21.77 ; $P = 0.0005$) and $+1.4$ (± 15.17 ; $P = 0.2142$) Early Treatment Diabetic Retinopathy Study letters, with mean number of injections of 5.2 and 3.4 in the treatment-naïve and prior-treated groups, respectively. VA gains were greater in patients with worse baseline VA, who received a loading dose, and with polypoidal choroidal vasculopathy (PCV). Multivariate logistic regression analyses demonstrated younger age, worse baseline VA, and those who received loading dose being associated with higher odds of any gain in VA at 1 year ($P < 0.05$). Mean CRT changes from baseline were -126.7 (± 174.90) μm ($P < 0.0001$) and $+10.8$ (± 89.52) μm ($P = 0.5833$) in the treatment-naïve and prior-treated groups, respectively, with greater reductions observed in patients with PCV. Ocular and non-ocular AEs were reported in 8.4% ($n=31$) and 10.1% ($n=37$) of patients, respectively. **Conclusion** The LUMINOUS study confirms real-world effectiveness and safety of ranibizumab in Korean patients with nAMD; factors including age, baseline VA, and loading-dose were associated with VA gain at one-year post-treatment.

Background

Age-related macular degeneration (AMD) is the most common cause of irreversible vision loss (1). The Korea National Health and Nutrition Examination Survey, conducted from 2008 to 2011, showed that the estimated prevalence of AMD in the Korean population aged ≥ 40 years is 6.62% (6.02% in early AMD and 0.60% in late AMD) (2). A nationwide population-based study conducted from 2008 to 2012 further showed that the prevalence of neovascular AMD (nAMD) in the Korean population aged

≥ 40 years was 0.36% (3). An effective treatment option is required to manage the disease burden associated with nAMD. The introduction of anti-vascular endothelial growth factors (anti-VEGFs) has transformed the management of nAMD, making anti-VEGFs the current standard of care for nAMD treatment (4).

Ranibizumab (Lucentis®; Novartis Pharma AG, Basel, Switzerland, and Genentech Inc., South San Francisco, CA, USA), is a humanised monoclonal antibody Fab fragment specifically designed for ocular use, which inhibits angiogenesis by binding with high affinity to all isoforms of VEGF-A (5). Ranibizumab was approved in Korea in 2007 for the treatment of patients with nAMD and is currently approved for the treatment of visual impairment due to nAMD, diabetic macular oedema (DME), macular oedema secondary to retinal vein occlusion (RVO), choroidal neovascularisation (CNV) secondary to pathologic myopia (PM), and CNV other than secondary to PM and nAMD (6).

Several studies have demonstrated the effectiveness and safety of ranibizumab in Korean patients with nAMD (7–9). A post hoc analysis of a ranibizumab post-marketing surveillance study in Korea demonstrated significant improvements in visual and anatomical outcomes after three-monthly ranibizumab injections (10). Despite these evidences, the long-term effectiveness and safety of intravitreal ranibizumab 0.5 mg in Korean patients with nAMD remains to be further explored.

LUMINOUS™ (NCT01318941) is the largest prospective observational study in the field of medical retina, designed to evaluate the long-term effectiveness, safety, and treatment patterns with ranibizumab in routine clinical practice across 5 approved indications (nAMD, DME, branch retinal vein occlusion [BRVO], central retinal vein occlusion [CRVO], myopic choroidal neovascularization [mCNV]) in Asia, Australia, Europe, and North and South America(11).

The Korea-specific 1- to 2-year effectiveness, treatment pattern, and overall safety outcomes in a subgroup of patients with nAMD enrolled in this study are reported here.

Methods

Ethics statement

The LUMINOUS study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, with any applicable national guidelines and ethical principles laid down in the Declaration of Helsinki. The study protocol was reviewed and approved by an Independent Ethics Committee or Institutional Review Board for each centre. Patients provided written informed consent. The study is registered with clinicaltrials.gov as NCT01318941 (www.clinicaltrials.gov).

Study design, study population and treatment protocol

LUMINOUS is a 5-year, prospective, observational, multicentre, open-label, single-arm, global study of ranibizumab 0.5 mg in patients with nAMD, DME, BRVO, CRVO, or mCNV. The study was conducted at 488 clinical sites across 42 countries (11).

Overall for the LUMINOUS study, consenting adult patients within the age limit as defined by local regulation (≥ 18 years) who were either treatment-naïve (i.e., patients who had not been pre-treated with any intravitreal medication in the primary treated eye), or prior-treated with ranibizumab or another ocular therapy for any of the approved indications included in the local ranibizumab label, were enrolled. Patients were excluded if they were participating in other investigational studies or if they had received systemic anti-VEGF therapy other than ranibizumab 90 days prior or ocular anti-VEGF therapy 30 days prior to enrolment. Patients were treated with intravitreal ranibizumab 0.5 mg according to the local product label at outpatient ophthalmology clinics.

Ranibizumab was re-administered according to the investigators' discretion, as needed. It was recommended to capture data at every visit or at least every 3 months. As patients were recruited over time and the calendar time point of study completion was pre-set, follow-up time varied according to the entry date. The minimum potential follow-up for each patient was identified as 1 year in the protocol. Patients who did not attend a follow-up visit at least once per year, or who were switched to another

anti-VEGF therapy, were discontinued from the study. The first eye treated was considered the primary treated eye. If both eyes were first treated on the same date, or if both eyes were pre-treated, the eye with the earliest diagnosis date was considered the primary treated eye.

The current subgroup analyses from the LUMINOUS study included Korean patients with nAMD who were treatment-naïve or prior-treated in their primary treated eye.

Study objective and assessments

The primary objective of the study, for all approved indications of ranibizumab in local product label, was to describe (i) the safety assessed by type, frequency, severity, and relationship of all non-ocular and ocular adverse events (AEs), and (ii) the effectiveness assessed by the mean change in VA over time and mean change in central retinal thickness (CRT) over time.

Demographic and baseline characteristics were collected at baseline, including ocular and non-ocular medical history, primary indication for initiation of ranibizumab treatment, and prior ocular treatments. Baseline lesion characteristics (lesion type, pigment epithelial detachment [PED], polypoidal choroidal vasculopathy [PCV], retinal angiomatous proliferation) for patients with nAMD were optional and collected if available, and were determined based on investigators' judgement. PCV was typically diagnosed based on the presence of active macular polypoidal lesions with indocyanine green angiography.

Effectiveness was assessed using VA as the functional parameter for all patients and CRT as the anatomical parameter on available data. VA, and preferably best-corrected visual acuity (BCVA), was evaluated from baseline at visits per the treating physician's discretion, using Early Treatment Diabetic Retinopathy Study (ETDRS)-like or Snellen charts. Snellen fractions and decimals were converted to the ETDRS equivalent letter scores to facilitate statistical analysis. Optical coherence tomography, to assess CRT, and ocular examination, to assess pre-injection intraocular pressure, were optional but included if the data were available. The number of ranibizumab injections administered overall, visit frequency, and treatment patterns were recorded. All AEs, irrespective of suspected causal association that occurred during the study, were collected.

Statistical analysis

All effectiveness and safety data were summarised descriptively. The enrolled set included all patients who signed the informed consent, and had at least a baseline assessment. The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment. The primary treated eye set included all primary treated eyes in patients included in the safety set, including both eyes that were

treatment-naïve or prior-treated. Patients with blindness recorded under their history or current medical conditions of the primary treated eye were excluded. For treatment-naïve eyes, the date of first on-study injection with ranibizumab was considered the baseline date. For prior-treated eyes that were previously treated with ranibizumab, the date of study entry was considered the baseline date. Patients were generally stratified based on pre-treatment status (treatment-naïve/prior-treated) for all safety and effectiveness analyses.

The loading dose was defined as receiving at least 3 ranibizumab injections within 120 days from baseline date. The mean change in VA from baseline at 1 year was analysed by loading dose status (yes/no), injection frequency (0–<3, 3–6, and >6), baseline VA category (< 23, 23–<39, 39–<60, 60–<74, and \geq 74 letters), and PCV status (PCV/non-PCV). To investigate factors associated with VA change, logistic regression analysis was performed to find the associated factors and their odds ratios with any VA improvement and \geq 5 letters improvement from baseline at 1 year. Predictors with a *P*-value < 0.05 in the univariate analysis were considered as significant, and were fitted into the multivariate logistic regression. Changes in CRT from baseline at 1 year was analysed by PCV status (PCV/non-PCV). Two-sided Student's *t* test was performed to compare demographics, characteristics, and mean change in VA and CRT between patient subgroups, and also to compare VA and CRT at baseline and Year 1. Statistical significance was considered to be a *P* value < 0.05. The number of injections and monitoring visits up to 1 year were summarised for patients with VA evaluated at 1 year. Safety over the 1- and 5-year periods was assessed based on the incidence, proportion, relationship, and severity of treatment-emergent ocular and non-ocular AEs. Ocular AEs were assessed for the primary treated eye set and non-ocular AEs were assessed for the safety set.

Results

Patient disposition, baseline ocular characteristics, and treatment patterns

The LUMINOUS study enrolled 30,138 patients across all approved indications worldwide (11). In this subgroup analysis, 367 Korean patients were enrolled. The safety set comprised 152 treatment-naïve and 215 prior-treated patients who were treated with \geq 1 dose of ranibizumab during the study or prior to study initiation and had \geq 1 safety assessment post-initial treatment. Overall, 159 (43.3%) patients discontinued the study by Year 1, of which 80 were treatment-naïve and 79 were prior-treated. In total, 265 (72.2%) patients discontinued from the study by the end of Year 2, of which 116 were treatment-naïve and 149 were prior-treated. The main reasons for study discontinuation were loss to follow-up and patient switching to another anti-VEGF (Fig. 1).

At baseline, the mean (SD) age was 72.2 (9.18) years in the treatment-naïve and 71.0 (8.20) years in the prior-treated patients. The majority of patients were male in both treatment-naïve (67.8%) and prior-treated (67.0%) patients. The patient demographics and baseline characteristics are summarised in

Table 1. Generally, all baseline lesion characteristics were comparable. Compared with prior-treated patients, treatment-naïve patients reported a lower mean (SD) VA (43.1 [26.30] vs 54.3 [21.29] letters,

Table 1
Baseline demographic, patient characteristics and treatment pattern at Year 1: Safety set and primary treated eye set

Characteristic	Overall N = 367	Treatment-naïve n = 152	Prior-treated n = 215	P-value ^a
Patient demographics				
Mean (SD) age, years	71.4 (8.63)	72.2 (9.18)	71.0 (8.20)	0.1907
Gender, n (%)				0.8743
Male	247 (67.3)	103 (67.8)	144 (67.0)	
Lesion characteristics				
CNV type, n (%)				0.4825
Predominantly classic	85 (23.2)	38 (25.0)	47 (21.9)	
Minimally classic/occult	282 (76.8)	114 (75.0)	168 (78.1)	
PED, n (%)	245 (66.8)	106 (69.7)	139 (64.7)	0.3083
PCV, n (%)	105 (28.6)	48 (31.6)	57 (26.5)	0.2900
RAP, n (%)	12 (3.3)	6 (3.9)	6 (2.8)	0.5394
Lesion size, %				0.1287
≤ 1 DA	135 (36.8)	49 (32.2)	86 (40.0)	
> 1 DA	232 (63.2)	103 (67.8)	129 (60.0)	
Ocular characteristics				
VA				
n	340	147	193	< 0.0001
Mean (SD), ETDRS letters	49.5 (24.19)	43.1 (26.30)	54.3 (21.29)	
CRT				
n	294	131	163	< 0.0001
Mean (SD), μm	338.5 (131.98)	400.3 (151.59)	288.8 (86.55)	
IOP				
n	303	125	178	0.1475
Mean (SD), mmHg	14.3 (3.60)	13.9 (3.75)	14.5 (3.49)	

The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment. Primary treated eye set included all primary treated eyes in patients included in the safety set

Indication and pre-treatment status refers to the primary treated eye

Patients with a baseline visit date on or before March 2015 were included. Data collected until the last recorded follow-up date were used to perform the analyses

^aTwo-sided student's t-test was performed to compare differences in baseline demographics and patient characteristics between treatment-naïve and prior-treated patients.

CRT, central retinal thickness; DA, disc area; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; N, total number of patients; n, number of patients;

nAMD, neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; SD, standard deviation; VA, visual acuity

Characteristic	Overall N = 367	Treatment-naïve n = 152	Prior-treated n = 215	P-value ^a
Treatment pattern				
Median time from diagnosis to first treatment, days (Q1, Q3)	59.0 (5.00, 264.00)	4.0 (1.00, 13.00)	199.0 (67.00, 557.00)	< 0.0001
Proportion of patients who had loading dose, n (%)	192 (52.32)	126 (82.9)	66 (30.7)	< 0.0001
Median time of follow-up, days (min, max)	426 (0, 1105)	312 (0, 1024)	442 (0, 1105)	0.0350
The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment. Primary treated eye set included all primary treated eyes in patients included in the safety set				
Indication and pre-treatment status refers to the primary treated eye				
Patients with a baseline visit date on or before March 2015 were included. Data collected until the last recorded follow-up date were used to perform the analyses				
^a Two-sided student's t-test was performed to compare differences in baseline demographics and patient characteristics between treatment-naïve and prior-treated patients.				
CRT, central retinal thickness; DA, disc area; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; N, total number of patients; n, number of patients;				
nAMD, neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; PED, pigment epithelial detachment; RAP, retinal angiomatous proliferation; SD, standard deviation; VA, visual acuity				

$P < 0.0001$) and thicker CRT (400.3 [151.59] vs 288.8 [86.55] μm , $P < 0.0001$) at baseline (Table 1). The median time from diagnosis to treatment was 4 days in treatment-naïve patients and 199 days in prior-treated patients ($P < 0.0001$). A total of 192 (53.32%) patients received the loading dose and the proportion of patients who received the loading dose was relatively higher in treatment-naïve patients (82.90%) compared with prior-treated patients (30.70%) ($P < 0.0001$). The median time of follow-up was 312 days in treatment-naïve patients and 442 days in prior-treated patients ($P = 0.0350$) (Table 1). The baseline demographics and characteristics of patients with and without PCV is shown in **Additional file 1: Table S1**.

Effectiveness outcomes

Visual acuity

Figure 2 shows the changes in mean VA for the primary treated eyes from baseline to 2 years. VA improvements were observed as early as 3 months post-baseline and treatment-naïve patients showed a higher VA gain compared with prior-treated patients (Fig. 2), a trend that was maintained from 3 to

21 months. At Month 24, there was a decline in the number of patients continuing in the study in both groups (treatment-naïve, $n = 20$; prior-treated, $n = 30$).

At Month 12 the mean VA significantly increase from baseline by + 10.1 (21.77) letters ($P = 0.0005$) in treatment-naïve patients, while the VA letter change was + 1.4 (15.17) letters ($P = 0.2141$) in prior-treated patients. The mean VA at Month 12 was comparable in both treatment-naïve (61.6 [23.31]) and prior-treated patients (57.4 [20.35]) (Fig. 3A). When stratified by baseline VA of < 23, 23–<39, 39–<60,

60–<74, and ≥ 74 letters, mean VA changes after 1 year of ranibizumab treatment were + 20.8, + 21.8, + 11.7, + 4.2, and – 1.9 letters in treatment-naïve patients, and + 21.0, + 5.1, + 2.0, + 0.4, and – 5.0 letters in prior-treated patients, respectively (Fig. 3B). When stratified by patients who did or did not receive the loading dose, mean VA changes after 1 year of ranibizumab treatment were + 10.2 and + 4.0 letters in treatment-naïve patients and + 6.0, and – 0.7 letters in prior-treated patients (Fig. 4A). When presented by injection frequencies over 1 year, the mean change in VA letter score was + 4.0, + 10.8, and + 8.0 in treatment-naïve patients who received 0–<3, 3–6, and > 6 injections, respectively. The mean change in VA letter score was lower in the prior-treated patients, with changes of + 2.8, + 0.4, and + 1.7 in patients who received 0–<3, 3–6, and > 6 injections, respectively (Fig. 4B).

When presented by PCV status, the mean change in VA was higher in the treatment-naïve patients with PCV (+ 16.7 letters) compared with those without (+ 6.7 letters), but was not statistically significant

($P = 0.1169$). Similarly, in prior-treated patients, the mean change in VA was higher in patients with PCV (+ 4.0 letters) versus those without (+ 0.5 letters, $P = 0.1958$). In the overall population, including both treatment-naïve and prior-treated patients, the difference in mean change was 6.5 letters (PCV vs

non-PCV = + 9.0 vs + 2.5 letters, $P = 0.0388$) (Fig. 5).

Association of baseline characteristics and visual outcomes

Univariate analysis showed that younger age ($P = 0.0087$), worse baseline VA ($P = 0.0131$), and patients who received a loading dose ($P = 0.0159$) were associated with a higher odds of any gain in VA by Month 12. Treatment-naïve ($P = 0.038$), worse baseline VA ($P = 0.0051$), and patients who received a loading dose ($P = 0.0010$) were associated with higher odds to gain ≥ 5 VA letters by Month 12. Multivariate analysis showed that younger age ($P = 0.0021$), worse baseline VA ($P = 0.0190$), and patients who received loading dose ($P = 0.0410$) were associated with higher odds of having any gain in VA by Month 12. However, only worse baseline VA ($P = 0.0313$) was associated with a better response to ranibizumab treatment for a gain of ≥ 5 VA letters (Table 2).

Table 2

Association of visual acuity change with baseline characteristics and treatment pattern in Korean patients with nAMD: Safety set and primary treated eye set

Baseline characteristics	Crude odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Any gain in VA at Month 12				
Age (years)	0.930 (0.8800, 0.9820)	0.0087	0.910 (0.8563, 0.9660)	0.0021
Age group (years)		0.7848		
50-<60	1322324.99 (0.0000)			
60-<70	1.815 (0.5150, 6.3920)			
70-<80	1.199 (0.3940, 3.6510)			
≥ 80	1.0 (Reference)			
Pre-treatment status				
Naïve	2.321 (0.9720, 5.5450)	0.0580		
Prior-treated	1.0 (Reference)			
VA (letters)	0.974 (0.9540, 0.9940)	0.0131	0.971 (0.9478, 0.9952)	0.0190
VA group (letters)		0.1149		
< 23	4.500 (0.8100, 24.9850)			
23-<39	5.000 (1.1630, 21.4990)			
39-<60	2.400 (0.8270, 6.9650)			
60-<74	1.333 (0.4560, 3.8990)			
≥ 74	1.0 (Reference)			
PCV				
Present	2.266 (0.8810, 5.8300)	0.0896		
Absent	1.0 (Reference)			
Loading dose status				
Loading	2.625 (1.1980, 5.7530)	0.0159	2.468 (1.0374, 5.8695)	0.0410
Non-loading	1.0 (Reference)			
Number of injections	1.077 (0.8960, 1.2940)	0.4306		
Number of visits	1.074 (0.8940, 1.2910)	0.4462		
Time from diagnosis to treatment range (days)		0.0866		
< 7	2.375 (0.6350, 8.8780)			
7-<30	1.250 (0.3130, 4.9980)			

The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment. The primary treated eye set included all primary treated eyes in patients included in the safety set

Covariates considered in the logistic regression modelling include baseline demographic, ocular characteristics, medical history and pre-treatment status. Predictors with *P* value less than 0.05 in the univariate analysis are considered as significant, and were fitted into the multivariate logistic regression

CI, confidence interval; nAMD, neovascular age-related macular degeneration OR, odds ratio; PCV, polypoidal choroidal vasculopathy; VA, visual acuity

Baseline characteristics	Crude odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
30-<90	1.143 (0.3550, 3.6760)			
90-<365	0.400 (0.1370, 1.1700)			
≥ 365	1.0 (Reference)			
Gain of at least 5 letters in VA at Month 12				
Age (years)	0.966 (0.9220, 1.0130)	0.1555		
Age group (years)		0.3819		
50-<60	3.888 (0.7180, 21.0520)			
60-<70	1.667 (0.4830, 5.7570)			
70-<80	1.238 (0.3990, 3.8410)			
≥ 80	1.0 (Reference)			
Pre-treatment status				
Naïve	3.250 (1.4620, 7.2220)	0.0038	1.818 (0.6641, 4.9761)	0.2447
Prior-treated	1.0 (Reference)			
VA (letters)	0.973 (0.9550, 0.9920)	0.0051	0.978 (0.9590, 0.9980)	0.0313
VA group (letters)		0.0446		
< 23	7.350 (1.5310, 35.2760)			
23-<39	6.600 (1.6940, 25.7100)			
39-<60	4.200 (1.2850, 13.7300)			
60-<74	4.200 (1.2340, 14.2930)			
≥ 74	1.0 (Reference)			
PCV		0.0811		
Present	2.088 (0.9130, 4.7750)			
Absent	1.0 (Reference)			
Loading dose status				
Loading	3.700 (1.6990, 8.0600)	0.0010	2.198 (0.8236, 5.8666)	0.1159
Non-loading	1.0 (Reference)			
Number of injections	1.139 (0.9560, 1.3560)	0.1455		
Number of visits	1.131 (0.9500, 1.3470)	0.1677		
Time from diagnosis to treatment range (days)		0.0634		

The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment. The primary treated eye set included all primary treated eyes in patients included in the safety set

Covariates considered in the logistic regression modelling include baseline demographic, ocular characteristics, medical history and pre-treatment status. Predictors with *P* value less than 0.05 in the univariate analysis are considered as significant, and were fitted into the multivariate logistic regression

CI, confidence interval; nAMD, neovascular age-related macular degeneration OR, odds ratio; PCV, polypoidal choroidal vasculopathy; VA, visual acuity

Baseline characteristics	Crude odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
< 7	3.239 (1.0410, 10.0740)			
7–<30	3.109 (0.8290, 11.6570)			
30–<90	1.583 (0.5240, 4.7800)			
90–<365	0.727 (0.2390, 2.2080)			
≥ 365	1.0 (Reference)			
The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment. The primary treated eye set included all primary treated eyes in patients included in the safety set				
Covariates considered in the logistic regression modelling include baseline demographic, ocular characteristics, medical history and pre-treatment status. Predictors with <i>P</i> value less than 0.05 in the univariate analysis are considered as significant, and were fitted into the multivariate logistic regression				
CI, confidence interval; nAMD, neovascular age-related macular degeneration OR, odds ratio; PCV, polypoidal choroidal vasculopathy; VA, visual acuity				

Treatment exposure and patient visits for patients with VA assessed at Year 1

Overall, in patients with VA assessed at Year 1, the mean (standard deviation [SD]) number of ranibizumab injections administered up to Year 1 was higher in treatment-naïve patients (5.2 [1.8]) compared with prior-treated patients (3.4 [2.1]). Similarly, the mean (SD) number of monitoring visits was also higher in treatment-naïve patients (9.2 [2.6]) compared with prior-treated patients (6.8 [2.8]). In the first year, the majority of treatment-naïve patients received ≥ 4 injections (77.3%), while only 44.2% of prior-treated patients received ≥ 4 injections (Fig. 6).

Central retinal thickness

Figure 7 shows the changes in mean CRT for the primary treated eyes from baseline to 2 years. Similar to VA improvement, reduction of CRT was observed as early as 3 months post-baseline and treatment-naïve patients showed a greater CRT reduction compared with prior-treated patients. This trend of better CRT improvement in treatment-naïve patients compared with prior-treated patients was maintained from 3 months to 2 years. At Month 12, the overall mean CRT reductions were – 126.7 (174.90) µm ($P < 0.0001$) in treatment-naïve patients and + 10.8 (89.62) µm ($P = 0.5833$) in prior-treated patients. The mean CRT at Month 12 was comparable for treatment-naïve (272.4 [83.82] µm) and prior-treated patients (292.0 [95.65] µm; **Additional file 2: Figure S2**).

When stratified by PCV and non-PCV, mean CRT changes after 1 year of ranibizumab treatment were – 160.6 µm and – 99.0 µm in treatment-naïve patients (mean differences in change: 61.6 µm) and – 14.9 µm and + 20.1 µm in prior-treated patients (mean difference in change: 35.0 µm). In the overall group, including both treatment-naïve and prior-treated patients, the mean differences in change between PCV and non-PCV patients was 69.4 µm ($P = 0.0293$; **Additional file 3: Figure S3**).

Safety outcomes

Over the 5-year period, the overall rate of ocular and non-ocular AEs in patients was 8.4% and 10.1%, respectively. **Additional file 4: Table S4** lists all ocular and non-ocular AEs by the end of the 5-year period. In treatment-naïve and prior-treated patients, ocular AEs were reported in 10.5% and 7.0% of patients, respectively. Conjunctival haemorrhage in 3 treatment-naïve patients (2.0%) and cataract in 1

treatment-naïve patient (0.7%) were suspected to be related to ocular injection and/or ranibizumab treatment (**Additional file 5: Table S5**). Non-ocular AEs were reported in 11.8% and 8.8% of treatment-naïve and prior-treated patients, respectively (**Additional file 4: Table S4**). No patients reported a

non-ocular AE suspected to be related to ocular injection and/or ranibizumab. **Additional file 6: Table S6** showed the rate of ocular and non-ocular AEs by preferred term by the end of Year 1.

Discussion

To our knowledge, the LUMINOUS subgroup analysis represents the first long-term study in Korean patients with nAMD assessing the real-world effectiveness and safety of ranibizumab 0.5 mg. The study findings demonstrated that ranibizumab 0.5 mg resulted in improved VA and CRT outcomes at the end of Year 2 in treatment-naïve patients. Also, by Year 1, patients who were treatment-naïve, those with worse baseline VA, and those who received loading dose achieved better VA outcome. In patients with PCV, better VA and CRT improvements were observed at the end of Year 1. Multivariate logistic regression analyses confirmed that younger age, worse baseline VA and those receiving a loading dose were associated with higher odds of having any gain in VA by Year 1. Overall, ranibizumab 0.5 mg was

well-tolerated with no new safety findings in the real-world setting, consistent with the findings of global LUMINOUS nAMD populations.

In the current study, 43.3% and 72.2% of patients discontinued by Years 1 and 2, respectively, with loss to follow-up and patient switching to another anti-VEGF being the main reasons for study discontinuation. This highlights poor compliance of patients returning to the clinic for follow-up, likely due to high treatment burden (12) or patient relocation and transfer to another healthcare facility. The high discontinuation rate was expected, and was aligned with real-world trends in Korea, that have also been reported in other real-world studies (13,14). In the current study, 28.9% of patients switched to

anti-VEGFs other than ranibizumab, and the majority were prior-treated. The 2019 Preferences and Trends Survey showed that 68.4% of Asia Pacific physicians would switch to another anti-VEGF when patients do not respond adequately to first-line anti-VEGF therapy (15). This switching is to potentially improve outcomes in patients who do not respond adequately to initial treatment, assuming potential differences in the molecular structure and biochemical properties of anti-VEGFs, and thus effect (16). In addition, when the LUMINOUS global study was conducted, the national health insurance system in Korea had set reimbursement limitations for ranibizumab injection. Thus, patients that required additional anti-VEGF treatment over and above the reimbursement limit might have switched to a more cost effective option, such as bevacizumab (off-label use) (10).

The proportion of male patients (67.3%) in the current study was consistent with the Korean

post-marketing surveillance (PMS) study which consisted of 62.5% of male patients with nAMD (10), and the nationwide population-based study which showed that prevalence of nAMD in Korea was higher in males in all age groups (3). Similarly, a real-world study in Japan showed a higher proportion of male patients with nAMD who were treated with anti-VEGFs (17). After comparing baseline characteristics of treatment-naïve patients in the Korean and global populations of the LUMINOUS study, it was observed that the former had a slightly lower baseline VA (43.1 letters vs 49.7 letters), higher baseline mean CRT values (400.3 μm vs 365.7 μm), a higher proportion of minimally classic/occult CNV lesion type (75.0% vs 55.4%), PED (69.7% vs 42.7%), and PCV (31.6% vs 9.2%) (11). In the current study, PCV was diagnosed in 28.6% of Korean patients with nAMD regardless of pre-treatment status. This observation is aligned with the finding that PCV prevalence was observed to be higher in the Asian population; PCV is shown to occur in approximately 22–55% of Asian and 4–14% of Caucasian patients with nAMD (18).

Both VA gain and reduction in CRT were most prominent at 3 months post-treatment in Korean patients, and this improvement was maintained up to 24 months. Both VA gain and CRT improvements were better in treatment-naïve patients compared with prior-treated patients. This result is consistent with findings from Levy et al (2009) (19), and the Korean PMS study (10), which demonstrated that prior-treated patients generally do not show as much response to anti-VEGFs as treatment-naïve patients.

Prior-treated patients had relatively better baseline VA and CRT, which would have likely benefitted from previous anti-VEGF treatment. Even though the VA gain and CRT reduction were better in treatment-naïve patients, both groups had comparable VA (61.6 vs 57.4 letters) and CRT (272.4 vs 292.0 μm) values at Year 1. The result was consistent with findings that ranibizumab 0.5 mg stabilises vision in nAMD patients with relatively good baseline VA (20,21). At Year 2, the greater VA gain of treatment-naïve patients than that of prior-treated patients was not maintained, which is likely due to large variations in VA between the low number of patients who remained in the study in both groups, and may not reflect the actual trend.

In Korean patients with VA assessed at Year 1, treatment-naïve patients received a higher number of injections (5.2) and recorded monitoring visits (9.2) by Year 1 compared with prior-treated patients

(3.4 injections, 6.8 visits). Compared with the global LUMINOUS treatment-naïve population, the Korean treatment-naïve patients reported comparable injection numbers (5.2 vs 5.0) and monitoring visits (9.2 vs 8.8), (11) yet with a relatively better VA outcome (VA gain of 10.1 vs 3.1 letters). The VA gain observed in prior-treated patients was consistent with that of the global population, whereby patients treated with ranibizumab maintained their vision at Year 1 (11,22). The better visual outcomes in treatment-naïve Korean patients compared with the treatment-naïve global population might also be attributed to a relatively younger age (72.2 vs 75.0 years), a worse baseline VA (43.1 vs 49.7 letters), and a shorter time from diagnosis to first treatment (4 days vs 12 days) (11,22). The VA gain reported in treatment-naïve patients in this subgroup analysis was comparable to those reported in the pivotal MARINA and ANCHOR studies (7.2 letters in MARINA (23) and 11.3 letters in ANCHOR (24)), but relatively higher than randomised controlled trials conducted in Korea and other real-world studies. Kim et al. (2016) demonstrated that treatment-naïve Korean patients with nAMD treated with a mean of 4.5 injections showed significant BCVA improvement (0.14 logMAR, $P=0.017$) and CRT reduction (139.3 μm , $P<0.001$) from baseline to Year 1 (7). In the REAL study conducted in Taiwanese patients with nAMD, the mean number of ranibizumab injections was 3.2, and the VA gain at 1 year was only 1.1 letters (25). The AURA study reported comparable injection numbers in Year 1 (5 injections) with VA gain of 2.4 letters (26). Similarly, the LUMIERE study reported a lower VA gain (3.2 letters) with a comparable number of injections (5.1) in Year 1 versus the current study (20). The UNCOVER study reported 4.2 injections and 7 visits per year with VA reduction of 0.7 letters in Year 1 (27). However, most of the pivotal trials and real-world studies did not stratify the results based on prior-treatment status. CRT reduction in treatment-naïve patients in this study (160.6 μm) was also better than other real-world studies of ranibizumab (51.5 μm in Providência et al, 2018) (28).

The median time from diagnosis to treatment in treatment-naïve patients in this subgroup analysis was relatively short (4 days) compared with the global LUMINOUS population (12 days) (11). Korean patients can easily visit retina clinics without referral from primary physicians, and the short distance from home to clinics or hospitals in Korea might enable early detection and timely treatment of nAMD patients. It has been established that delay from symptoms to anti-VEGF treatment is associated with reduced VA outcome (29). Timely initiation of anti-VEGF treatment might also explain the favourable visual outcome in the Korean nAMD population in the current study compared with the LUMINOUS global population, as well as other real-world studies.

Stratified by different baseline characteristics and treatment categories, it was demonstrated that in both treatment-naïve and prior-treated patients, those with worse baseline vision (< 23 letters and 23–<39 letters), those who received the loading-dose, and those with PCV achieved higher VA gain by Year 1. Although VA improvement at Year 1 was notably higher in treatment-naïve compared with prior-treated patients, univariate logistic regression analyses did not support the association of pre-treatment status to any gain of VA, but showed that treatment-naïve patients have higher odds of achieving a VA gain of ≥ 5 letters by Year 1. However, multivariate logistic regression analysis showed that only patients with younger age, worse baseline VA, and those who received a loading dose were associated with higher odds of any gain in VA by Year 1, while only patients with worse baseline VA was associated with VA gain of ≥ 5 letters in Year 1.

Younger age as a prediction factor for better response to ranibizumab treatment is in-line with the Korean PMS study (10) and several post hoc analyses of pivotal trials and studies assessing predictors of response to ranibizumab (30–35). Findings from the current study also strengthen the observation regarding baseline VA being an important factor in predicting visual outcome, consistent with the Korean PMS study, (10) the study by Pedrosa et al. (2016) (36), the LUMIERE study (20), and the global LUMINOUS study (11,22). These findings could be explained by the “ceiling effect” whereby patients with higher baseline VA have limited potential to gain more letters, while those with lower baseline VA have little possibility for further loss of vision. However, patients with higher baseline VA had relatively higher mean VA by the end of Year 1; i.e. the VA at Year 1 were highest in patients with baseline VA of ≥ 74 letters in both treatment-naïve and prior-treated patients. The result indicated that even though eyes with poor VA responded well to treatment, they did not catch up to eyes with better baseline VA.

Additionally, Korean patients who received the loading dose showed better VA improvement compared with those who did not, which is consistent with the BeMOc study (21), the real-world LUMIERE study (20), and the global LUMINOUS study (11). It should also be noted that in both

treatment-naïve and prior-treated groups, patients who received a loading dose had worse baseline VA compared with patients who did not. However, multivariate analyses adjusted for age and baseline VA confirmed that receiving a loading dose is associated with any gain in VA in Year 1. Findings from LUMINOUS highlighted the importance of the loading dose for VA improvements. This was not aligned with findings from the ARTIS study which showed that ranibizumab treatment regimens with 1 and 3 initial injections followed by a pro re nata regimen are equally effective in improving VA (37).

Treatment-naïve Korean patients with PCV showed a VA gain of 16.7 letters by Year 1, which is notably higher than patients without PCV (6.7 letters). Treatment-naïve patients with PCV also reported a greater reduction in CRT ($-160.6 \mu\text{m}$) compared with non-PCV patients ($-99.0 \mu\text{m}$). The findings were in line with those from the global LUMINOUS treatment-naïve population with PCV (38). VA gain and CRT reduction in the Korean treatment-naïve patients with PCV (16.7 letters and $160.6 \mu\text{m}$) was better than the global treatment-naïve population with PCV (5.0 letters and $91.3 \mu\text{m}$) (38). The better visual outcome in treatment-naïve Korean patients with PCV compared with the treatment-naïve global population with PCV might be due to a relatively younger age (68.4 vs 72.8 years) and a worse baseline VA (49.0 vs 53.8 letters) (38). However, due to a small sample size and large variance in the current subgroup analyses, no statistically significant difference was noted in the differences in changes in VA and CRT between treatment-naïve PCV and non-PCV patients ($P > 0.05$). Nonetheless, when VA and CRT were compared between patients with and without PCV in the overall group including both treatment-naïve and prior-treated patients, the differences in mean change was statistically significant for both VA ($P = 0.0388$) and CRT ($P = 0.0293$) at Year 1. In this subgroup analyses, PCV patients were relatively younger compared with patients without PCV (treatment-naïve: 68.4 vs 73.9 years, $P = 0.0514$; prior-treated: 68.7 vs 71.8 years; $P = 0.8609$); this is in line with previous studies that showed PCV tends to present in younger Asian patients compared with typical CNV (39–41). In fact, univariate and multivariate logistic regression analysis did not support an association of having PCV with any VA gain or gain of ≥ 5 letters at Year 1. The age difference between the PCV and non-PCV patients in this subgroup analyses might have driven the differences in the outcome at Year 1. It should be noted that fibrosis or haemorrhage in patients with PCV are usually observed with long-term follow-up, and might not be reflected over 1 year; thus it remained indefinite if the improved VA gain in PCV patients might be maintained beyond 1 year (42).

In both treatment-naïve and prior-treated Korean patients with nAMD in this subgroup analyses, the frequency of ocular and non-ocular AEs over 1 and 5 years was low, and were consistent with the well-established safety profile of ranibizumab with no new safety findings identified (10,23,24). Ocular AEs related to ranibizumab treatment and/or ocular injection were rare. There was no significant difference in the rate of ocular and systemic AEs between the treatment-naïve and prior-treated patients.

The current study had various limitations. The high discontinuation rate only allowed the treatment effectiveness to be meaningfully analysed up to 2 years. Being a real-life study, there was no comparator arm. There could be treatment bias due to patient's access to treatment, physicians' treatment decisions based on clinical judgement, local healthcare systems, and reimbursement policies, which limit interpretation of data to some extent. Besides, there were no strict criteria for disease diagnosis at the time of patient enrolment; hence, results may vary between study sites. Most of the limitations described are common to any real-world evidence study which collect real-world clinical practice data. The low number of patients with PCV also limits confirmation on the effect of ranibizumab in treatment-naïve Korean patients with nAMD and PCV, and requires to be validated in a prospective study with larger sample size and longer follow-up period.

Conclusions

To conclude, real-world evidence from the LUMINOUS subgroup analysis in Korean patients with nAMD confirmed the long-term effectiveness and safety of ranibizumab 0.5 mg for the treatment of nAMD, including PCV. In addition, Korean patients achieved better effectiveness outcomes compared with the global population, with a comparable number of injections and patient clinic visits in Year 1. The safety findings were consistent with the well-established safety profile of ranibizumab. The current study findings may help ophthalmologists to understand treatment outcomes in real-world clinical practice in Korean nAMD patients and assist in optimising the treatment and clinical management of the disease.

Abbreviations

AEs: adverse events; AMD: Age-related macular degeneration; Anti-VEGF: anti-vascular endothelial growth factor; BCVA: best corrected visual acuity; BRVO: branch retinal vein occlusion; CI: confidence interval; CNV: choroid neovascularization; CRVO: central retinal vein occlusion; CRT: central retinal thickness; DME: diabetic macular edema; EDTRS: Early Diabetic Treatment Retinopathy Study; IOP: intraocular pressure; mCNV: myopic choroidal neovascularization; nAMD: neovascular age related macular degeneration; OR: odds ratio; PCV: polypoidal choroidal vasculopathy; PED: pigment epithelial detachment; PM: pathologic myopia; PMS: post-marketing surveillance; RAP: retinal angiomatous proliferation; RVO: retinal vein occlusion; SD: standard deviation; SE: standard error; VA: visual acuity

Declarations

Ethics approval and consent to participate

The LUMINOUS study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, with any applicable national guidelines and ethical principles laid down in the Declaration of Helsinki. The study protocol was reviewed and approved by an Independent Ethics Committee or Institutional Review Board for each centre. Patients provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Youkyung Lee is a full time employee of Novartis Korea.

Se Joon Woo is a paid consultant of Samsung Bioepis Inc., Songdo, South Korea; Panolos Bioscience Inc., Seoul, South Korea; Novelty Nobility Inc., Seoul, South Korea and is a co-founder of RetiMark Inc., in Seoul, South Korea.

Min Sagong has nothing to disclose.

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Author's contribution

Min Sagong: Substantial contributions to the conception and design of protocol, acquisition, analysis and interpretation of data for the subgroup analyses; drafting, and critical review and revision of the manuscript.

Se Joon Woo: Substantial contributions to the conception and design of protocol, acquisition, analysis and interpretation of data for the subgroup analyses; drafting, and critical review and revision of the manuscript.

Youkyung Lee Woo: Substantial contributions to the acquisition, analysis and interpretation of data for the subgroup analyses; drafting, and critical review and revision of the manuscript.

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Figures

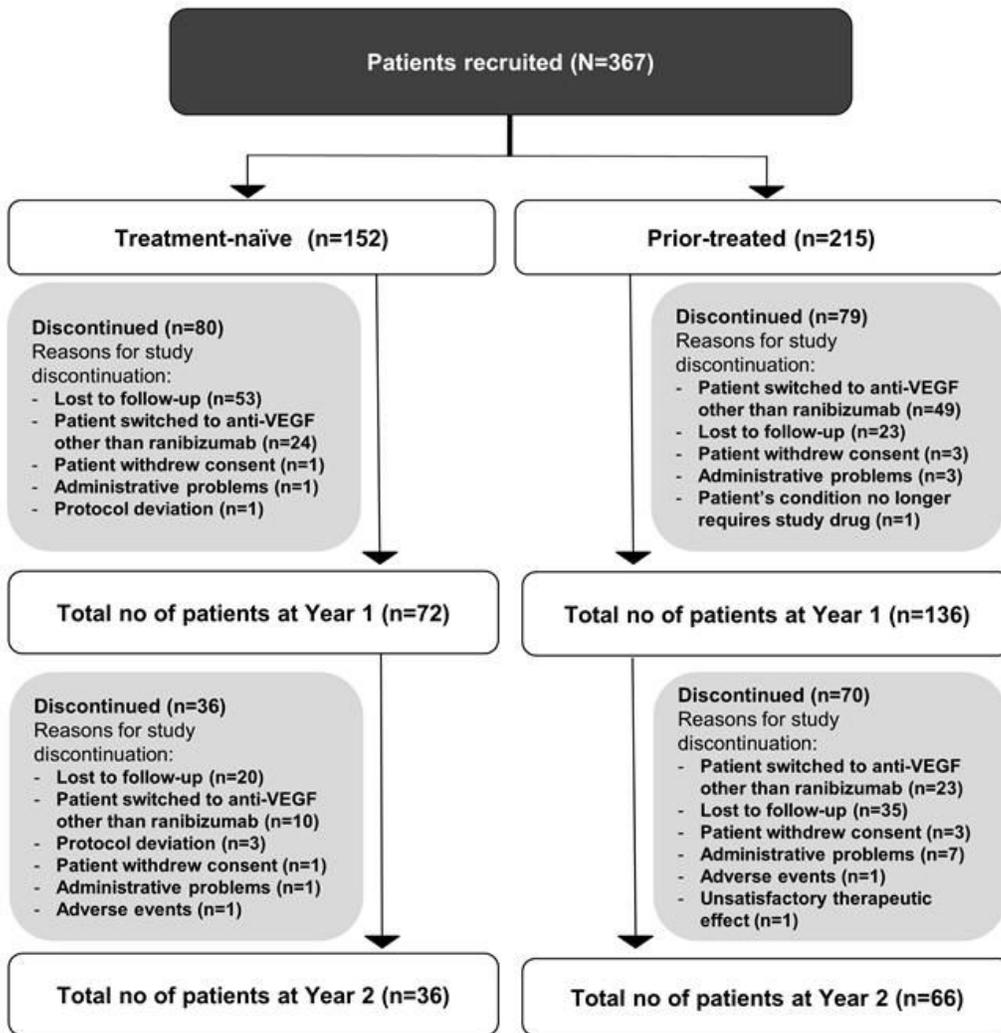
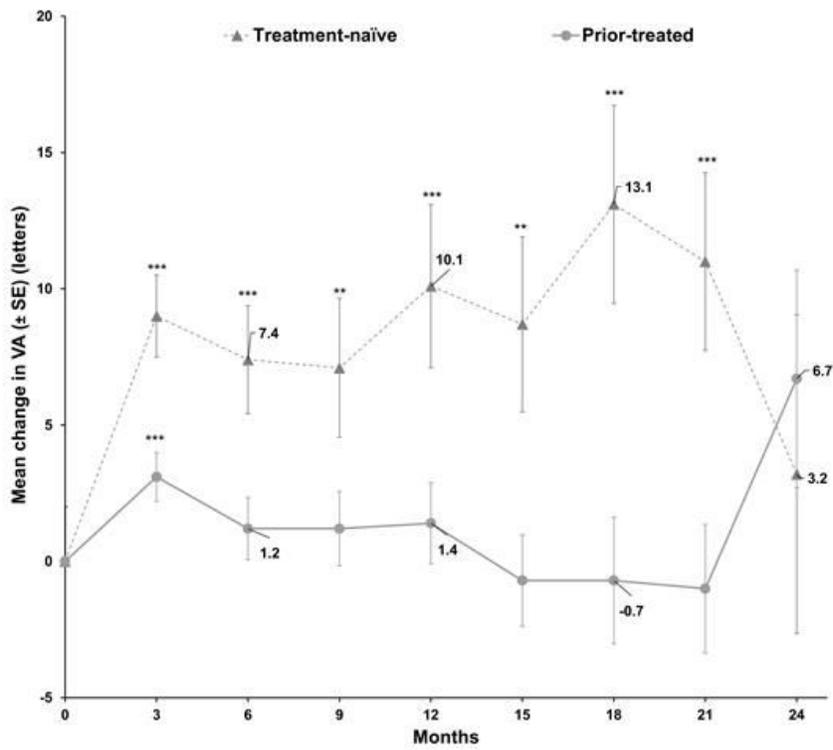


Figure 1

Disposition of Korean patients with nAMD The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment Patients with a baseline visit on or before March 2015 were included N, total number of patients; n, number of patients; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor



Treatment-naïve, n	147	129	87	67	53	45	39	32	20
Prior-treated, n	193	170	134	122	104	85	62	48	30

Figure 2

Mean change from baseline in visual acuity (ETDRS letter score): Primary treated eye set Primary treated eye set included all primary treated eyes in patients included in the safety set Mean ± SE was presented. The study entry date was defined as baseline date if the primary-treated eye has been pre-treated with ranibizumab. If the eyes were not pre-treated with ranibizumab, the date of the first on-study ranibizumab injection was considered as the baseline date Statistical analyses were performed using two-sample Student's t-tests to compare VA between baseline and specific time point, **P < 0.01, ***P < 0.001 ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity; n, number of patients, SE, standard error

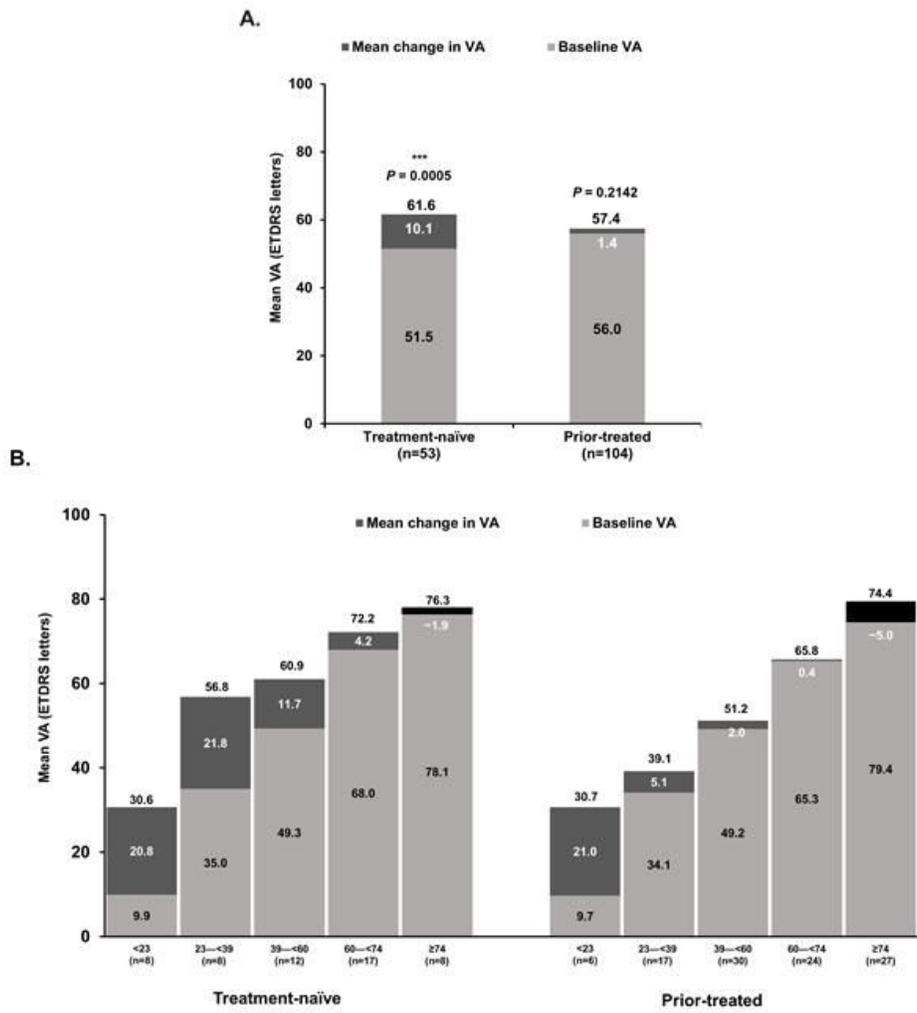


Figure 3

Mean change in VA from baseline to Month 12 in primary treated eye set by (A) Pre-treatment status; (B) Baseline VA Observed data set for VA change in primary treated eye set. Primary treated eye set included all primary treated eyes in patients included in the safety set. Statistical analyses were performed using two-sample Student's t-tests to compare VA between baseline and Year 1, ***P < 0.001 ETDRS, Early Treatment Diabetic Retinopathy Study; n, number of patients; VA, visual acuity

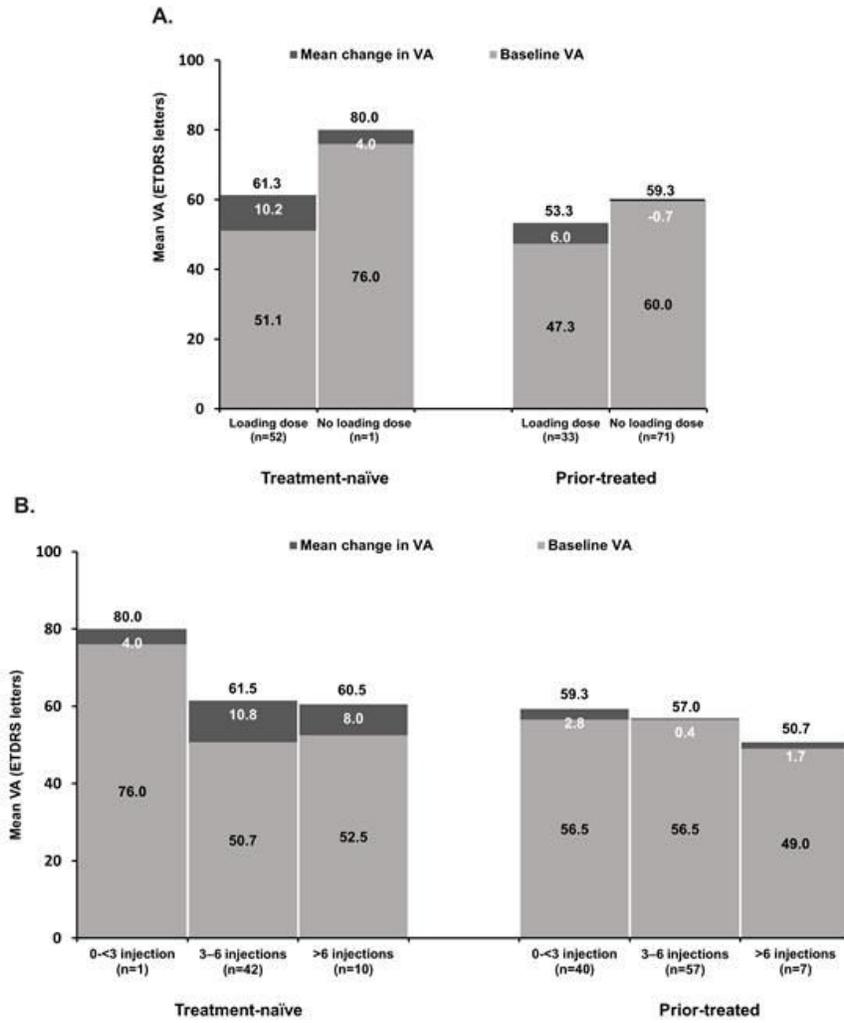


Figure 4

Mean change in VA from baseline to Month 12 in primary treated eye set by (A) Loading dose status (B) Injection number Observed data set for VA change in primary treated eye set. Primary treated eye set included all primary treated eyes in patients included in the safety set. Loading dose was defined as receiving at least three ranibizumab injection within 120 days from baseline date ETDRS, Early Treatment Diabetic Retinopathy Study; n, number of patients; VA, visual acuity

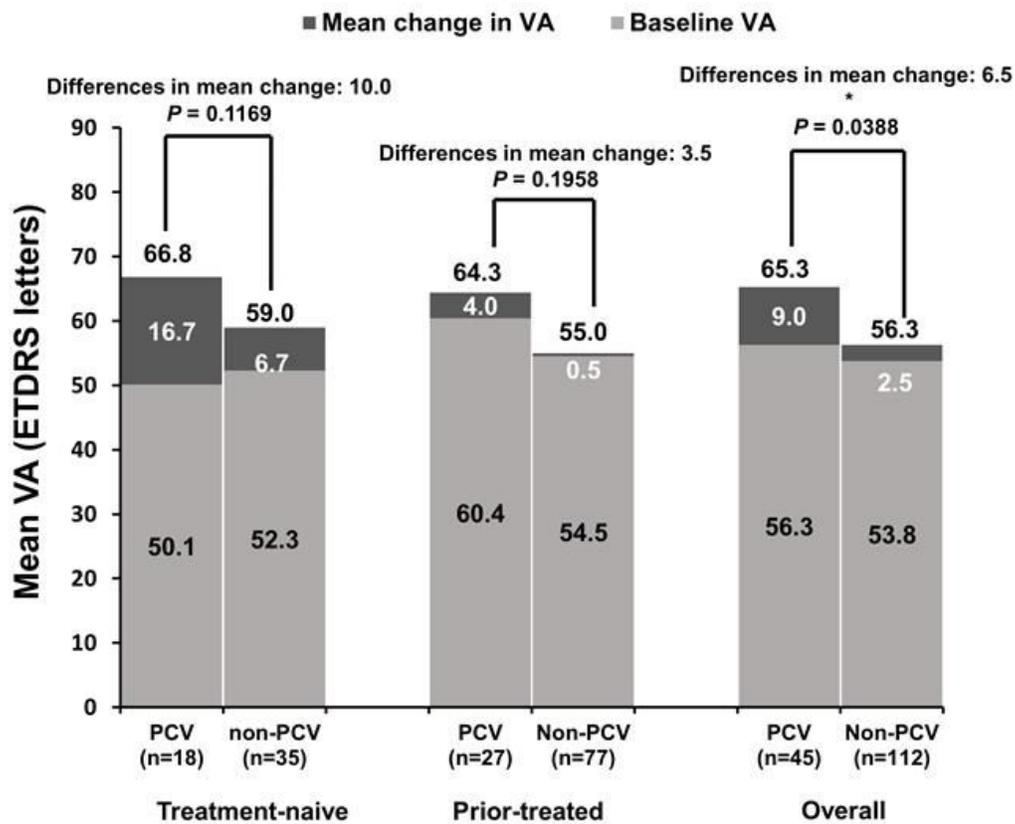
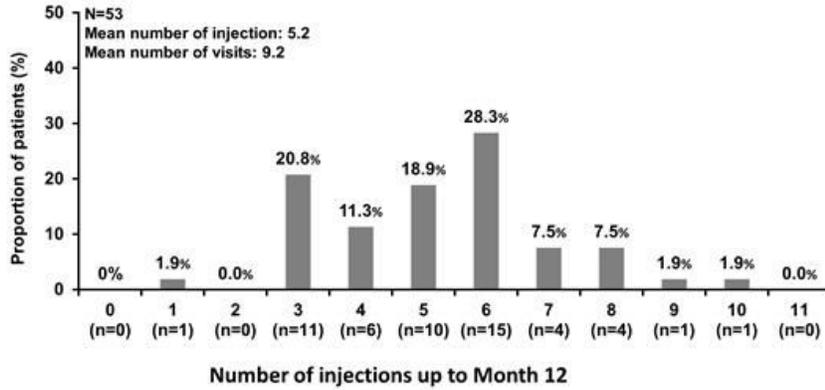


Figure 5

Mean change in VA from baseline to Month 12 by PCV status: Primary treated eye set Observed data set for VA change in primary treated eye set. Primary treated eye set included all primary treated eyes in patients included in the safety set Statistical analyses were performed using two-sample Student's t-tests to compare the mean change in VA between patients with/ without PCV, *P < 0.05 ETDRS, Early Treatment Diabetic Retinopathy Study; n, number of patients; PCV, polypoidal choroidal vasculopathy; VA, visual acuity

A.



B.

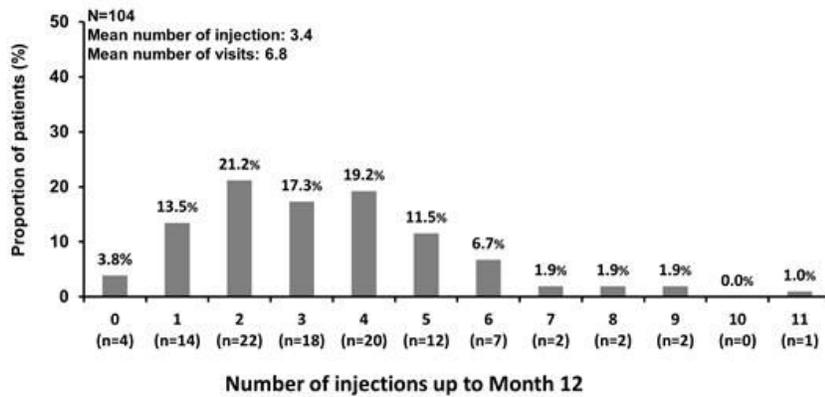
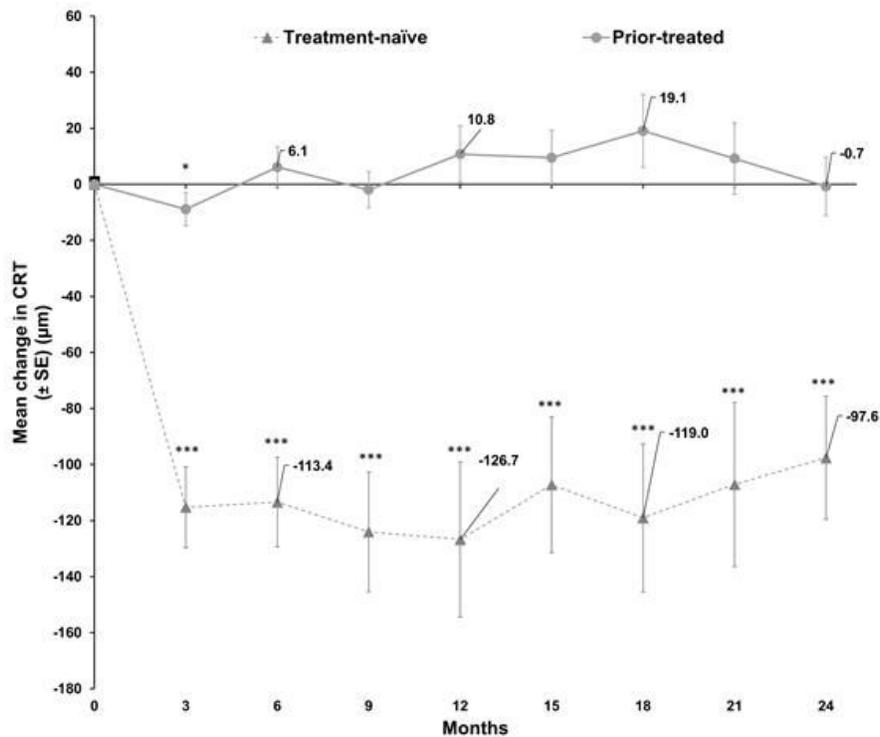


Figure 6

Frequency of visit and injections over 12 months in Korean patients with nAMD and VA assessed at Month 12 in primary-treated eye and safety sets (A) Treatment-naïve patients; (B) Prior-treated patients The safety set comprised patients in the enrolled set who were treated with at least one dose of ranibizumab during the study or prior to study initiation and had at least one safety assessment post-initial treatment. Primary treated eye set included all primary treated eyes in patients included in the safety set n, number of evaluable patients with baseline and Month 12 data; nAMD, neovascular age-related macular degeneration



Treatment-naïve, n	131	105	68	53	40	36	32	24	15
Prior-treated, n	163	131	102	93	79	68	51	40	22

Figure 7

Mean change from baseline in CRT (μm): Primary treated eye set Primary treated eye set included all primary treated eyes in patients included in the safety set Mean \pm SE was presented. The study entry date was defined as baseline date if the primary-treated eye has been pre-treated with ranibizumab. If the eyes were not pre-treated with ranibizumab, the date of the first on-study ranibizumab injection was considered as the baseline date Statistical analyses were performed using two-sample Student's t-tests to compare CRT between baseline and specific time point, **P < 0.01, ***P < 0.001. CRT, central retinal thickness; n, number of patients; SE, standard error

Supplementary Files

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