



## OPEN Real-world outcomes of ranibizumab biosimilars in various retinal diseases: a Korean multi-center experience—ROSE Korea Study

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This study aims to investigate efficacy and safety of ranibizumab biosimilars (Amelivu<sup>®</sup> and LucenBS<sup>®</sup>) across retinal diseases in Korean clinical practice. This retrospective, multicenter study enrolled 1153 eyes from 1075 patients across five centers in South Korea between May 2022 and October 2024. Patients received intravitreal ranibizumab biosimilars for neovascular age-related macular degeneration, retinal vein occlusion with macular edema, diabetic macular edema, and other retinal diseases. Treatment-naïve eyes comprised 408 cases (35.4%), while 745 eyes (64.6%) had prior anti-VEGF treatment. Amelivu was administered to 1007 eyes with 3.1 ± 1.9 injections over 10.2 ± 6.1 months; LucenBS to 146 eyes with 3.1 ± 2.0 injections over 12.0 ± 4.9 months. Amelivu demonstrated significant BCVA(logMAR) improvements from baseline (0.63 ± 0.62) to 12 months (0.55 ± 0.61,  $P < 0.01$ ). LucenBS maintained logMAR VA from 0.64 ± 0.63 to 0.63 ± 0.68 at 12 months ( $P = 0.40$ ). Both biosimilars achieved significant CMT reductions through 12 months: Amelivu from 398.0 ± 169.4 μm to 323.0 ± 128.8 μm ( $P < 0.01$ ); LucenBS from 368.7 ± 172.0 μm to 306.0 ± 144.1 μm ( $P < 0.01$ ). Treatment-naïve eyes showed superior CMT reduction (111.8 μm) compared to previously treated eyes (53.5 μm). Only one injection-related adverse event occurred: asymptomatic anterior chamber cells in the Amelivu group, resolving with topical treatment. Ranibizumab biosimilars demonstrated visual stabilization and significant anatomical improvements across retinal diseases with excellent safety profiles.

**Keywords** Anti-VEGF agents, Biosimilars, Diabetic macular edema, Neovascular age-related macular degeneration, Retinal vein occlusion

Retinal Vascular diseases including neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), retinal vein occlusion (RVO) and myopic macular neovascularization (m-MNV) remains a leading cause of vision loss worldwide. These diseases are driven by vascular endothelial growth factor (VEGF), for which anti-VEGF agents have become the mainstay of treatment<sup>1</sup>. Among these, ranibizumab (Lucentis<sup>®</sup>),

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a humanized monoclonal antibody fragment targeting all isoforms of VEGF-A, has demonstrated substantial efficacy in improving and maintaining visual acuity across multiple pivotal trials, including the MARINA and ANCHOR studies for AMD<sup>2–4</sup>, BRAVO and CRUISE study for RVO<sup>5</sup>, and RISE/RIDE study for DME<sup>6</sup>. However, the economic burden associated with long-term use of originator biologics like ranibizumab (Lucentis, Genentech, USA) has posed significant challenges to sustained therapy and affordable access, particularly in resource-constrained settings<sup>7</sup>.

To address these challenges, biosimilars have been developed as potentially cost-effective alternatives that exhibit high similarity to their reference biologics in terms of quality, efficacy, and safety, supported by comprehensive analytical and clinical comparability studies<sup>8</sup>. Several ranibizumab biosimilars, including SB11 (Byooviz®[US/EU]/Amelivu®[KR]; Samsung Bioepis, South Korea), FYB201(Cimerli® [US]/Ranivisio® [EU]; Bioeq [Formycon/Polpharma Biologics]), CKD-701(LucenBS®; Chong Kun Dang), and QL1205 (Rimmyrah® [EU]; Qilu Pharmaceutical), have demonstrated equivalence to reference ranibizumab in phase 3 randomized controlled trials. These trials have led to approvals by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and the Ministry of Food and Drug Safety (MFDS) in South Korea<sup>9–12</sup>. These biosimilars typically offer a cost reduction of 20–30% compared to the originator product, which can have a significant impact on healthcare resource allocation and patient access to anti-VEGF therapy<sup>13</sup>. Nevertheless, there remains limited availability of multicenter real-world data evaluating the clinical performance of these biosimilar candidates across diverse clinical environments. The expanding anti-VEGF biosimilar landscape, including recent aflibercept biosimilars following market exclusivity expiration in 2024, further emphasizes the critical need for comprehensive real-world evidence<sup>14</sup>. However, while several studies have examined India-specific ranibizumab biosimilars in real-world settings, there remains limited evidence for FDA/EMA/MFDS-approved biosimilars, which undergo more strict regulatory evaluation and have broader global applicability. Our study addresses this critical evidence gap by evaluating FDA/EMA/MFDS-approved biosimilars in a large, multi-center Asian cohort.

In South Korea, two prominent ranibizumab biosimilars have gained regulatory approval and clinical attention: Amelivu (Samsung Bioepis, South Korea), approved by the Ministry of Food and Drug Safety (MFDS) in 2022<sup>9,15,16</sup>, and LucenBS (Chong Kun Dang, South Korea)<sup>11</sup>, which has been developed as part of the expanding biosimilar landscape. While these agents have demonstrated analytical and clinical similarity to reference ranibizumab through comprehensive comparability studies, real-world evidence from multicenter clinical practice remains essential to establish their performance in routine clinical settings. Previous biosimilar perception studies and surveys of ophthalmologists from various regions, including India, the US, UK, and Europe (such as the Bio-INDAS and Bio-USER surveys), have shown that clinicians prefer real-world data over biosimilar trial data. This highlights the importance of post-marketing surveillance and real-world evidence in guiding clinical practice decisions<sup>17</sup>.

Given the critical need for comprehensive real-world evidence supporting the clinical application of ranibizumab biosimilars, the present multicenter study aims to investigate the efficacy and safety of Amelivu and LucenBS in five clinical centers across various indications. This approach provides valuable insights into the real-world performance of these biosimilars across different practice patterns, patient populations, and clinical environments, contributing to the growing body of evidence supporting the use of biosimilars in retinal diseases while addressing clinicians' interest for post-marketing real-world data of ranibizumab biosimilar drugs. This study is a part of the initiative taken by the International Retina Biosimilar Study Group (Inter-BIOS Group).

## Methods

This retrospective, multicenter study was conducted across four major tertiary hospitals and one specialized ophthalmology hospital in South Korea: Seoul National University Bundang Hospital, Seoul National University Hospital, Kim's Eye Hospital, Severance Hospital at Yonsei University, and Yeungnam University Medical Center. The study protocol was approved by the Institutional Review Board of each participating institution and conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived by the Institutional Review Boards.

## Study participants

We included all eyes that received intravitreal ranibizumab biosimilar injections between May 2022 and October 31, 2024, with a minimum follow-up period of one month. This retrospective study included all consecutive patients meeting eligibility criteria during the study period. Given the real-world evidence nature of this analysis, formal a priori sample size calculation was not performed. Instead, we included all eligible eyes that received ranibizumab biosimilar injections during the study period. A total of 1153 eyes from 1075 patients were enrolled across the five medical centers. The baseline was defined as the date of the first intravitreal biosimilar ranibizumab injection during the study period.

Two ranibizumab biosimilar formulations were used: Amelivu® (10 mg/mL, Samsung Bioepis, South Korea) and LucenBS® (10 mg/mL, Chong Kun Dang, South Korea). Amelivu® was administered in all five centers (1,007 eyes, 87.3%), while LucenBS® was used in two centers only (146 eyes, 12.7%). Treatment was administered according to either pro re nata (PRN) or treat-and-extend (T&E) protocols based on the treating physician's clinical judgment and institutional preferences.

Participants were categorized into two groups based on their anti-VEGF treatment history: treatment-naïve eyes, defined as those receiving their first anti-VEGF therapy, and previously treated eyes, defined as those previously treated with other anti-VEGF agents. For previously treated patients, we systematically collected detailed information regarding the last anti-VEGF injection type, total number of previous anti-VEGF injections, and duration of previous treatment. Moreover, when switching from reference ranibizumab or other anti-VEGF

agents to biosimilar ranibizumab, no washout period was required. The switch occurred at the next scheduled treatment visit, reflecting standard real-world clinical practice.

### Outcome measures

Visual and anatomical outcomes were evaluated at baseline, 1, 3, 6, and 12 months, and at the last visit. Best-corrected visual acuity (BCVA) was measured using standardized protocols and converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letters or logarithm of the minimum angle of resolution (LogMAR) units for analysis. Optical coherence tomography (OCT) examinations were performed using spectral-domain OCT to assess central macular thickness (CMT) and the presence of intraretinal fluid (IRF) and subretinal fluid (SRF). A “dry macula” was defined as the absence of both SRF and IRF. CMT was derived from automated segmentation of spectral-domain OCT devices at each center, with manual correction of segmentation errors by experienced retina specialists when necessary. IRF, SRF, and dry macula status were assessed by retina specialists at each institution.

Safety profiles were comprehensively evaluated through systematic retrospective chart review including clinical examination notes, fundus photography, and optical coherence tomography images to identify injection-related adverse events. Fluorescein angiography findings were incorporated when available. We specifically monitored endophthalmitis and other forms of intraocular inflammation, retinal tears, retinal detachment, retinal hemorrhage, increased intraocular pressure, and systemic adverse events. For each adverse event, detailed information was recorded including timing of occurrence, type of complication, severity, and treatment administered. The relationship between adverse events and biosimilar ranibizumab injection was determined by qualified ophthalmologists through systematic review of medical records and clinical assessment to distinguish injection-related complications from other causes.

### Data collection

Baseline characteristics collected included demographic information, disease characteristics, previous treatment history, and insurance coverage status. Follow-up data included duration of follow-up after biosimilar ranibizumab injection, total number of injections administered during the study period, treatment response, and need for additional therapies. Treatment switches to alternative therapies were performed at the clinical judgment of the treating physician based on individual patient response and clinical assessment.

### Statistical analysis

Statistical analyses were performed using Python 3.11.13 and GraphPad Prism software (GraphPad Software Inc, San Diego, CA). Normality of continuous variables was assessed using the Shapiro–Wilk test. Descriptive statistics were presented as mean  $\pm$  standard deviation for continuous variables and frequencies with percentages for categorical variables. Between-group comparisons and changes from baseline were analyzed using independent t-tests or Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables, as appropriate based on data distribution. Paired t-tests or Wilcoxon signed-rank tests were used to compare baseline and follow-up values within the same group. A P value of less than 0.05 was considered statistically significant for all analyses.

## Results

### Baseline characteristics

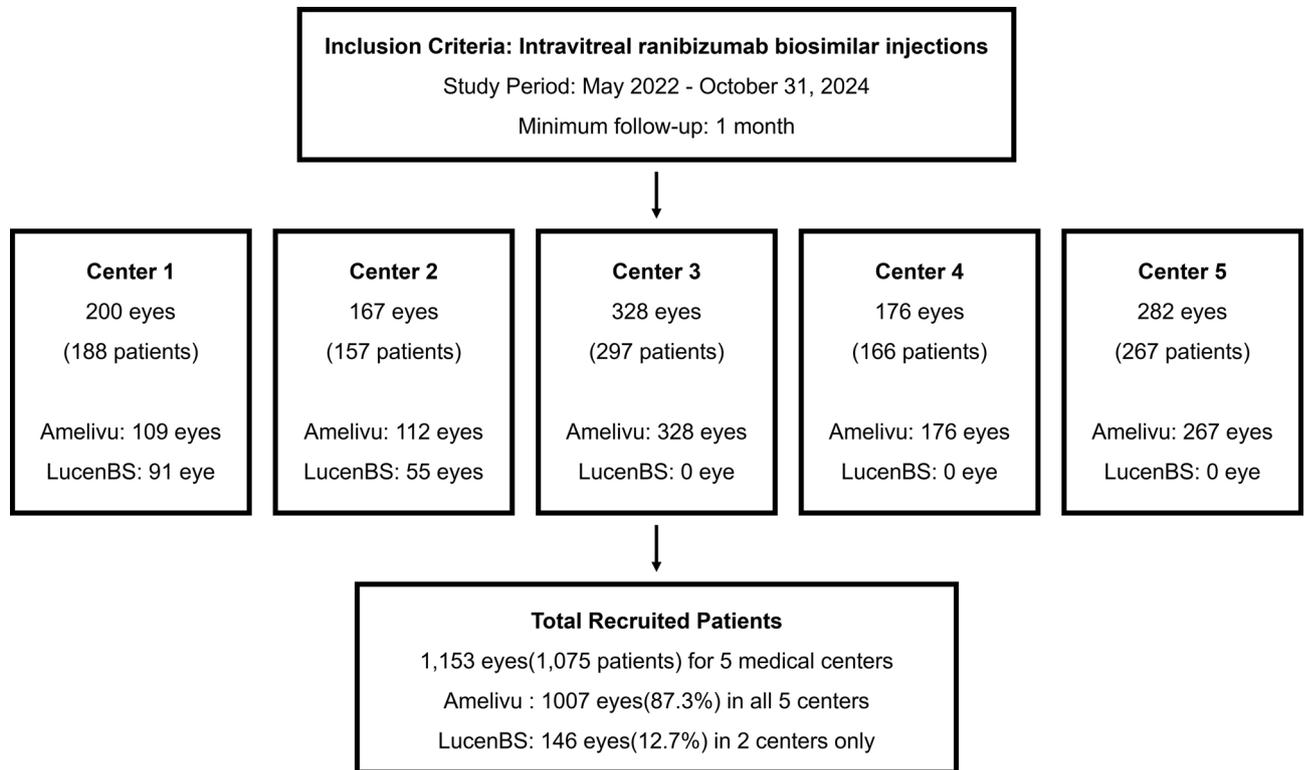
A total of 1153 eyes from 1075 patients were enrolled across five medical centers between May 2022 and October 31, 2024 (Fig. 1). During the study period, a total of 3575 intravitreal ranibizumab biosimilar injections were administered. The mean age was  $67.7 \pm 13.6$  years, and 539 patients (46.7%) were male. The most common indications were nAMD in 498 eyes (43.2%), RVO with macular edema (ME) in 246 eyes (21.3%), and DME in 133 eyes (11.5%). Treatment-naïve eyes comprised 408 cases (35.4%), while 745 eyes (64.6%) had prior anti-VEGF treatment with a mean of  $11.3 \pm 12.0$  previous injections over  $50.9 \pm 99.8$  months. Among previously treated eyes, the most frequent last anti-VEGF agent was bevacizumab (68.3%), followed by aflibercept (11.8%) and ranibizumab (11.2%), while brolocizumab and dexamethasone implant were used in less than 3% of cases. During follow-up, 51.8% of Amelivu-treated eyes and 70.5% of LucenBS-treated eyes maintained the initial biosimilar without treatment exchange (Table 1). Among eyes requiring treatment modification, aflibercept biosimilar (Afilivu) was the most common subsequent therapy (20.1% for Amelivu group, 17.8% for LucenBS group), followed by aflibercept (Eylea, 7.3% and 2.8%, respectively) (Table 2).

Amelivu was administered to 1,007 eyes (87.3%) across all five centers, with patients receiving a mean of  $3.1 \pm 1.9$  injections over  $10.2 \pm 6.1$  months of follow-up. LucenBS was used in 146 eyes (12.7%) at two centers only, with patients receiving a mean of  $3.1 \pm 2.0$  injections over  $12.0 \pm 4.9$  months of follow-up ( $P < 0.01$  for follow-up duration). The LucenBS group was significantly older ( $70.2 \pm 12.4$  vs  $67.4 \pm 13.8$  years,  $P = 0.02$ ), had a higher proportion of previously treated eyes (74.0% vs 63.3%,  $P = 0.01$ ), and lower insurance coverage rates (24.7% vs 31.3%,  $P < 0.01$ ). Baseline visual acuity was similar between groups ( $0.6 \pm 0.6$  vs  $0.6 \pm 0.6$  logMAR,  $P = 0.92$ ), while central macular thickness showed a trend toward difference ( $368.7 \pm 172.0$  vs  $398.0 \pm 169.4$   $\mu\text{m}$ ,  $P = 0.06$ ) (Table 1).

### Efficacy profile: visual and anatomical outcomes

#### Visual acuity changes

Amelivu demonstrated significant BCVA (logMAR) improvements from baseline ( $0.63 \pm 0.62$ ,  $n = 1004$ ) to 12 months ( $0.55 \pm 0.61$ ,  $n = 467$ ,  $P < 0.01$ ), with the greatest improvement observed at 6 months ( $0.53 \pm 0.57$ ,  $n = 754$ ). In contrast, LucenBS showed no significant visual improvements from baseline ( $0.64 \pm 0.63$ ,  $n = 146$ ) to 12 months ( $0.63 \pm 0.68$ ,  $n = 118$ ,  $P = 0.40$ , Table 3, Fig. 2A).



**Fig. 1.** Patient recruitment and distribution flow chart of intravitreal ranibizumab biosimilar injections across five tertiary medical centers. This study included patients who received intravitreal ranibizumab biosimilar injections between May 2022 and October 31, 2024, with a minimum follow-up period of one month. A total of 1,153 eyes from 1075 patients across five medical centers were recruited. Amelivu was administered in all five centers (1007 eyes, 87.3%), whereas LucenBS was used only in two centers (146 eyes, 12.7%).

Disease-specific response patterns varied significantly across indications. nAMD patients treated with Amelivu showed significant visual improvements at early time points (1, 3, and 6 months, all  $P < 0.01$ ), though statistical significance was not maintained at 12 months ( $P = 0.06$ ). LucenBS-treated nAMD patients showed no significant visual changes at any time point. RVO ME patients demonstrated the most favorable outcomes with both treatments. Amelivu achieved sustained significant visual improvements from 1 month through 6 months (all  $P < 0.01$ ), while LucenBS showed significant improvements at discrete time points: 1 month ( $P = 0.01$ ) and 12 months ( $P < 0.01$ ), but not at intermediate time points. DME patients showed limited visual responses with both biosimilars. Amelivu produced significant early improvement only at 1 month ( $P = 0.02$ ), while LucenBS showed no consistent pattern of significant visual improvement across any time point.

Treatment history significantly influenced visual outcomes. Treatment-naïve patients treated with Amelivu achieved significant visual improvements from baseline  $0.56 \pm 0.57$  ( $n = 370$ ) that were sustained at all time points through 12 months ( $0.39 \pm 0.46$  at 12 months,  $n = 190$ , all  $P < 0.01$ ). Previously treated eyes with Amelivu showed significant improvements only through 6 months ( $P < 0.01$ ), but not at 12 months ( $P = 0.23$ ). Treatment-naïve patients treated with LucenBS ( $n = 38$  at baseline) showed no significant visual improvements at any time point, with BCVA changing from baseline  $0.44 \pm 0.45$  to  $0.36 \pm 0.37$  logMAR at 12 months ( $n = 25$ ,  $P = 0.70$ ). Previously treated LucenBS eyes ( $n = 108$  at baseline) similarly showed no significant visual changes (baseline  $0.71 \pm 0.67$  to 12 months  $0.71 \pm 0.73$  logMAR,  $n = 93$ ,  $P = 0.34$ ) (Table 4).

#### Anatomical outcomes

Both biosimilars achieved significant and sustained central macular thickness reductions throughout the study period (Table 3, Fig. 2B). Amelivu reduced CMT from baseline  $398.0 \pm 169.4$   $\mu\text{m}$  ( $n = 965$ ) with significant improvements maintained from 1 month through 12 months ( $323.0 \pm 128.8$   $\mu\text{m}$  at 12 months,  $n = 454$ , all  $P < 0.01$ ). LucenBS similarly demonstrated significant CMT reductions from baseline  $368.7 \pm 172.0$   $\mu\text{m}$  ( $n = 141$ ) at all time points through 12 months ( $306.0 \pm 144.1$   $\mu\text{m}$  at 12 months,  $n = 113$ , all  $P < 0.01$ ).

When analyzed by indication, both biosimilars showed consistent anatomical responses across disease types. nAMD patients treated with Amelivu demonstrated sustained CMT reductions from  $379.9 \pm 163.8$   $\mu\text{m}$  at baseline to  $322.2 \pm 133.9$   $\mu\text{m}$  at 12 months ( $P < 0.01$ ). LucenBS-treated AMD patients showed changes from  $312.0 \pm 171.4$   $\mu\text{m}$  to  $278.6 \pm 152.9$   $\mu\text{m}$  at 12 months ( $P = 0.17$ ). RVO ME patients achieved pronounced anatomical improvements with both biosimilars, with Amelivu reducing CMT from  $480.8 \pm 206.1$   $\mu\text{m}$  to  $326.7 \pm 132.9$   $\mu\text{m}$  at 12 months ( $P < 0.01$ ) and LucenBS from  $483.3 \pm 175.2$   $\mu\text{m}$  to  $335.2 \pm 174.6$   $\mu\text{m}$  ( $P < 0.01$ ). DME patients

Characteristics	Total	Amelivu	LucenBS	P-value
Number of eyes (patients)	1153	1007	146	–
Age, mean $\pm$ SD (years)	67.7 $\pm$ 13.6	67.4 $\pm$ 13.8	70.2 $\pm$ 12.4	0.02
Male, n (%)	539 (46.7%)	475 (47.2%)	64 (43.8%)	0.02
DM	439 (38.6%)	390 (39.4%)	49 (33.6%)	0.61
HTN	498 (44.0%)	440 (44.6%)	58 (39.7%)	0.05
Bilateral injection of RBZ, n (%)	156 (13.5%)	131 (13.0%)	25 (17.1%)	0.27
Baseline VA (logMAR), mean $\pm$ SD	0.6 $\pm$ 0.6	0.6 $\pm$ 0.6	0.6 $\pm$ 0.6	0.92
Baseline CST, mean $\pm$ SD, $\mu$ m	394.2 $\pm$ 169.9	398.0 $\pm$ 169.4	368.7 $\pm$ 172.0	0.06
Indication				
AMD	498 (43.2%)	431 (42.8%)	67 (45.9%)	
RVO ME	246 (21.3%)	215 (21.4%)	31 (21.2%)	
DME	133 (11.5%)	102 (10.1%)	31 (21.2%)	
PDR VH	117 (10.1%)	117 (11.6%)	0 (0.0%)	
Myopic CNV	97 (8.4%)	86 (8.5%)	11 (7.5%)	
Other CNV	62 (5.4%)	56 (5.6%)	6 (4.1%)	
Insured, n (%)	351 (30.4%)	315 (31.3%)	36 (24.7%)	<0.01
Treatment naïve, n (%)	408 (35.4%)	370 (36.7%)	38 (26.0%)	0.01
Previously treated, n (%)	745 (64.6%)	637 (63.3%)	108 (74.0%)	
Number of injections prior to RBZ biosimilar, mean $\pm$ SD	11.3 $\pm$ 12.0	11.5 $\pm$ 12.1	10.1 $\pm$ 11.8	0.27
Time interval of RBZ biosimilar after initial anti-VEGF, mean $\pm$ SD, months	50.9 $\pm$ 99.8	52.7 $\pm$ 106.9	39.7 $\pm$ 34.3	0.02
Type of last injection				
Avastin	509 (68.9%)	437 (69.0%)	72 (67.9%)	
Eylea	88 (11.9%)	69 (10.9%)	19 (17.9%)	
Lucentis	83 (11.2%)	72 (11.4%)	11 (10.4%)	
Beovu	21 (2.8%)	17 (2.7%)	4 (3.8%)	
LucenBS	2 (0.3%)	2 (0.3%)	0 (0.0%)	
Maquaid	14 (1.9%)	14 (2.2%)	0 (0.0%)	
Vabysmo	6 (0.8%)	6 (0.9%)	0 (0.0%)	
Ozurdex	7 (0.9%)	7 (1.1%)	0 (0.0%)	
Unknown	9 (1.2%)	9 (1.4%)	0 (0.0%)	
Total RBZ biosimilar injections during FU period, mean $\pm$ SD	3.1 $\pm$ 1.9	3.1 $\pm$ 1.9	3.1 $\pm$ 2.0	0.87
Total FU duration, mean $\pm$ SD, months	10.4 $\pm$ 6.0	10.2 $\pm$ 6.1	12.0 $\pm$ 4.9	<0.01

**Table 1.** Baseline characteristics of patients treated with ranibizumab biosimilars. Data are presented as mean  $\pm$  standard deviation for continuous variables and as number (percentage) for categorical variables. AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CMT, central macular thickness; DME, diabetic macular edema; DM, diabetes mellitus; HTN, hypertension; logMAR, logarithm of the minimum angle of resolution; PDR VH: Proliferative diabetic retinopathy with vitreous hemorrhage; RBZ, ranibizumab; RVO ME, retinal vein occlusion macular edema; SD, standard deviation. Statistical comparisons were performed using independent t-test for continuous variables and chi-square test for categorical variables.

demonstrated significant CMT reductions with Amelivu from 458.0  $\pm$  153.8  $\mu$ m to 374.2  $\pm$  167.2  $\mu$ m at 12 months ( $P < 0.01$ ).

Both treatment-naïve and previously treated eyes achieved significant anatomical improvements with both biosimilars (Table 4). Treatment-naïve eyes demonstrated substantial CMT reductions from higher baseline values (421.4  $\pm$  202.9  $\mu$ m to 309.6  $\pm$  138.9  $\mu$ m at 12 months,  $P < 0.01$ ), while previously treated eyes showed consistent improvements from their baseline measurements (379.1  $\pm$  146.4  $\mu$ m to 325.6  $\pm$  127.5  $\mu$ m at 12 months,  $P < 0.01$ ).

### Optical coherence tomography fluid parameters

Significant improvements in retinal fluid parameters were observed across both biosimilars, though with varying patterns by indication (Supplementary Table 1, Fig. 3). In AMD patients treated with Amelivu, there was a significant decrease in IRF from baseline 45.6% maintained through 12 months (34.2%,  $P < 0.01$ ), and SRF decreased from 62.2 to 34.2% at 12 months ( $P < 0.01$ ). Dry macula achievement improved significantly from 15.2% at baseline to 44.4% at 12 months ( $P < 0.01$ ). LucenBS-treated AMD patients showed IRF changes from 37.3 to 34.5% at 12 months, while SRF decreased from 43.3 to 27.3% ( $P = 0.10$ ), and dry macula achievement changed from 28.4 to 45.5% ( $P = 0.08$ ).

RVO ME patients showed the most dramatic fluid improvements with both biosimilars. Amelivu-treated patients achieved significant reductions in IRF from 91.5 to 52.0% at 12 months ( $P < 0.01$ ) and SRF from 32.4 to

Exchange/subsequent therapies	Amelivu (n, %)	LucenBS (n, %)
No exchange	522 (51.8%)	103 (70.5%)
Afilivu	202 (20.1%)	26 (17.8%)
Eylea	74 (7.3%)	4 (2.8%)
LucenBS	39 (3.9%)	0 (0.0%)
Avastin	59 (5.9%)	3 (2.1%)
Beovu	32 (3.2%)	3 (2.1%)
Vabysmo	16 (1.6%)	4 (2.7%)
Lucentis	9 (0.9%)	1 (0.7%)
Ozurdex	15 (1.5%)	0 (0.0%)
IVTA	7 (0.7%)	2 (1.4%)
Laser treatment	32 (3.2%)	0 (0.0%)

**Table 2.** Exchange and subsequent therapies after injection of ranibizumab biosimilars. Distribution of exchange or subsequent therapies in all patients, stratified by ranibizumab biosimilar type (Amelivu vs. LucenBS). Values are presented as count (percentage).

6.9% ( $P < 0.01$ ). Dry macula achievement increased substantially from 5.6 to 48.0% ( $P < 0.01$ ). LucenBS-treated RVO ME patients similarly demonstrated significant improvements, with IRF decreasing from 93.5 to 60.9% at 12 months ( $P < 0.01$ ) and dry macula achievement increasing from 3.2 to 39.1% ( $P < 0.01$ ).

DME patients showed more modest fluid improvements. Amelivu-treated patients demonstrated IRF reduction from 97.1% at baseline to 82.9% at 12 months ( $P < 0.01$ ) and dry macula achievement improvement from 2.9 to 17.1% ( $P < 0.01$ ). LucenBS-treated DME patients showed IRF changes from 89.7 to 84.0% at 12 months and dry macula changes from 6.9 to 16.0%. Representative OCT images demonstrating baseline anatomical findings and treatment response at 1 month across major indications are shown in Fig. 4.

### Safety profile

The safety profiles of both ranibizumab biosimilars were excellent with minimal adverse events. In the Amelivu group (1007 eyes), only one injection-related adverse event occurred: asymptomatic anterior chamber cells developed 42 days after the seventh injection in one patient. This resolved completely following topical treatment with prednisolone acetate and levofloxacin. The LucenBS group (146 eyes) had no reported injection-related adverse events throughout the study period. No cases of endophthalmitis, retinal detachment, retinal tears, or other serious ocular complications occurred in either group. No systemic adverse events related to ranibizumab biosimilar treatment were identified during the study period.

### Comparative analysis between biosimilars

Visual outcomes showed significant differences favoring Amelivu at 6 months in the total cohort ( $P = 0.02$ ) and in DME patients ( $P = 0.02$ ) (Table 3). Anatomical outcomes demonstrated variable patterns depending on indication, with both biosimilars achieving significant CMT reductions from their respective baseline values. LucenBS group had significantly different baseline characteristics including older age (70.2 vs 67.4 years), higher proportion of previously treated eyes (74.0% vs 63.3%), and treatment at only two specialized centers. However, observed differences in treatment outcomes between LucenBS and Amelivu do not necessarily indicate differences in drug efficacy. Rather, they reflect the inherent characteristics of real-world evidence studies. These characteristics include differential drug accessibility, cost considerations and institutional practice patterns across healthcare facilities.

### Discussion

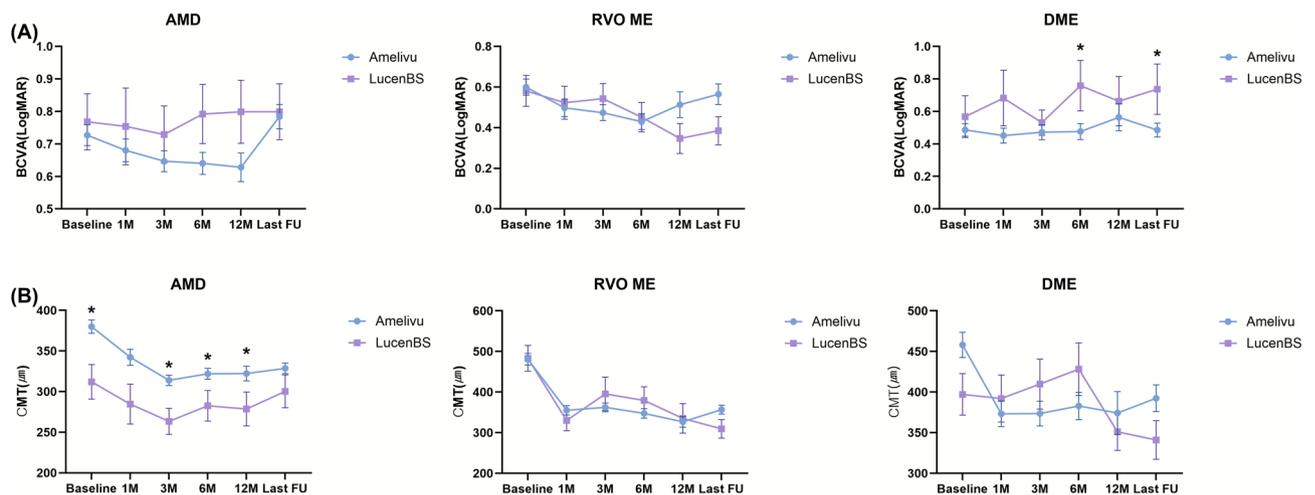
In this multicenter, retrospective real-world cohort study including 1,153 eyes from 1,075 patients across four tertiary medical centers and one specialized ophthalmology hospital, we analyzed treatment outcomes of ranibizumab biosimilars (Amelivu and LucenBS). Both biosimilars demonstrated clinically meaningful anatomical improvement and visual stabilization or improvement across approved indications. CMT decreased significantly and durably through 12 months, OCT fluid parameters improved across all indications. Moreover, outcome patterns were broadly consistent across major indications (nAMD, DME, and RVO-ME). Treatment-naïve eyes generally showed earlier and greater improvements than previously treated eyes, consistent with expectations from chronic disease biology and prior exposure to anti-VEGF agents. Importantly, no significant new adverse events emerged, reinforcing the clinical feasibility of biosimilar adoption in routine practice. Taken together, these real-world outcomes demonstrate the effectiveness and safety of ranibizumab biosimilars in heterogeneous clinical settings.

Multiple phase 3 randomized trials have established equivalence of ranibizumab biosimilars to the reference product across visual and anatomical endpoints with comparable safety and immunogenicity profiles. FYB201 met prespecified equivalence margins under fixed monthly dosing through 48 weeks, demonstrating overlapping BCVA trajectories and CMT reductions compared to reference ranibizumab<sup>10</sup>. SB11 similarly satisfied visual equivalence criteria with sustained 1-year outcomes and comparable safety<sup>15,18</sup>. The PRN-designed CKD-701 trial confirmed equivalence under a regimen closer to real-world practice, showing similar BCVA gains,

Indication/outcome	Timepoint	Total	Amelivu	P-value	LucenBS	P-value	P-value†
Total							
BCVA (LogMAR)	Baseline	0.64 ± 0.62 (n = 1150)	0.63 ± 0.62 (n = 1004)	–	0.64 ± 0.63 (n = 146)	–	0.92
	1 month	0.56 ± 0.60 (n = 910)	0.56 ± 0.59 (n = 804)	< 0.01	0.64 ± 0.67 (n = 106)	0.46	0.19
	3 months	0.56 ± 0.58 (n = 1026)	0.55 ± 0.59 (n = 896)	< 0.01	0.60 ± 0.56 (n = 130)	0.44	0.31
	6 months	0.55 ± 0.59 (n = 879)	0.53 ± 0.57 (n = 754)	< 0.01	0.67 ± 0.65 (n = 125)	0.79	0.02
	12 months	0.56 ± 0.63 (n = 585)	0.55 ± 0.61 (n = 467)	< 0.01	0.63 ± 0.68 (n = 118)	0.40	0.18
	Last FU	0.64 ± 0.65 (n = 935)	0.64 ± 0.65 (n = 791)	0.10	0.64 ± 0.68 (n = 144)	0.96	0.89
CMT (µm)	Baseline	394.23 ± 169.93 (n = 1106)	397.96 ± 169.39 (n = 965)	–	368.69 ± 172.03 (n = 141)	–	0.06
	1 month	337.00 ± 150.09 (n = 880)	338.28 ± 150.18 (n = 784)	< 0.01	326.55 ± 149.76 (n = 96)	< 0.01	0.47
	3 months	330.39 ± 132.92 (n = 983)	331.48 ± 128.89 (n = 861)	< 0.01	322.69 ± 158.85 (n = 122)	< 0.01	0.49
	6 months	330.52 ± 132.19 (n = 849)	331.01 ± 128.73 (n = 732)	< 0.01	327.45 ± 152.69 (n = 117)	0.01	0.79
	12 months	319.63 ± 131.98 (n = 567)	323.01 ± 128.75 (n = 454)	< 0.01	306.04 ± 144.05 (n = 113)	< 0.01	0.22
	Last FU	333.54 ± 137.42 (n = 1102)	337.05 ± 137.29 (n = 969)	< 0.01	307.90 ± 136.11 (n = 133)	< 0.01	0.22
AMD							
BCVA (LogMAR)	Baseline	0.73 ± 0.67 (n = 496)	0.73 ± 0.66 (n = 429)	–	0.77 ± 0.71 (n = 67)	–	0.64
	1 month	0.69 ± 0.65 (n = 383)	0.68 ± 0.64 (n = 339)	< 0.01	0.75 ± 0.78 (n = 44)	0.42	0.48
	3 months	0.66 ± 0.64 (n = 453)	0.65 ± 0.63 (n = 393)	< 0.01	0.73 ± 0.68 (n = 60)	0.45	0.36
	6 months	0.66 ± 0.64 (n = 401)	0.64 ± 0.63 (n = 341)	< 0.01	0.79 ± 0.71 (n = 60)	0.78	0.09
	12 months	0.66 ± 0.68 (n = 282)	0.63 ± 0.66 (n = 226)	0.06	0.80 ± 0.73 (n = 56)	0.99	0.09
	Last FU	0.79 ± 0.70 (n = 425)	0.78 ± 0.70 (n = 360)	0.11	0.80 ± 0.70 (n = 65)	0.65	0.87
CMT (µm)	Baseline	370.66 ± 166.33 (n = 479)	379.88 ± 163.84 (n = 414)	–	311.97 ± 171.36 (n = 65)	–	< 0.01
	1 month	336.37 ± 177.39 (n = 373)	342.24 ± 179.35 (n = 335)	< 0.01	284.63 ± 151.52 (n = 38)	0.01	0.06
	3 months	307.19 ± 122.67 (n = 434)	313.95 ± 121.52 (n = 376)	< 0.01	263.38 ± 122.09 (n = 58)	< 0.01	< 0.01
	6 months	315.83 ± 125.46 (n = 388)	321.91 ± 120.73 (n = 328)	< 0.01	282.55 ± 145.38 (n = 60)	0.16	0.03
	12 months	313.55 ± 138.67 (n = 273)	322.18 ± 133.90 (n = 219)	< 0.01	278.56 ± 152.93 (n = 54)	0.17	0.04
	Last FU	324.81 ± 136.54 (n = 477)	328.55 ± 132.38 (n = 414)	< 0.01	300.29 ± 160.27 (n = 63)	0.20	0.13
RVO ME							
BCVA (LogMAR)	Baseline	0.60 ± 0.56 (n = 246)	0.60 ± 0.58 (n = 215)	–	0.58 ± 0.42 (n = 31)	–	0.86
	1 month	0.50 ± 0.54 (n = 197)	0.50 ± 0.56 (n = 172)	< 0.01	0.52 ± 0.40 (n = 25)	0.01	0.83
	3 months	0.48 ± 0.53 (n = 226)	0.47 ± 0.55 (n = 198)	< 0.01	0.54 ± 0.40 (n = 28)	0.26	0.52
	6 months	0.43 ± 0.49 (n = 193)	0.43 ± 0.51 (n = 167)	< 0.01	0.45 ± 0.37 (n = 26)	0.24	0.83
	12 months	0.48 ± 0.60 (n = 125)	0.51 ± 0.64 (n = 102)	0.16	0.35 ± 0.36 (n = 23)	< 0.01	0.23
	Last FU	0.54 ± 0.61 (n = 192)	0.56 ± 0.64 (n = 161)	0.10	0.39 ± 0.39 (n = 31)	< 0.01	0.13
CMT (µm)	Baseline	481.09 ± 202.08 (n = 241)	480.76 ± 206.13 (n = 210)	–	483.32 ± 175.15 (n = 31)	–	0.95
	1 month	351.95 ± 147.68 (n = 193)	355.03 ± 150.80 (n = 169)	< 0.01	330.25 ± 124.10 (n = 24)	< 0.01	0.44
	3 months	366.40 ± 157.45 (n = 216)	362.41 ± 149.23 (n = 190)	< 0.01	395.58 ± 209.34 (n = 26)	0.02	0.32
	6 months	351.53 ± 149.41 (n = 186)	347.38 ± 147.23 (n = 162)	< 0.01	379.58 ± 163.99 (n = 24)	0.04	0.33
	12 months	328.29 ± 140.76 (n = 124)	326.71 ± 132.87 (n = 101)	< 0.01	335.22 ± 174.55 (n = 23)	< 0.01	0.80
	Last FU	350.82 ± 154.92 (n = 237)	356.80 ± 158.09 (n = 207)	< 0.01	309.53 ± 125.58 (n = 30)	< 0.01	0.12
DME							
BCVA (LogMAR)	Baseline	0.51 ± 0.49 (n = 133)	0.49 ± 0.40 (n = 102)	–	0.57 ± 0.71 (n = 31)	–	0.41
	1 month	0.50 ± 0.52 (n = 96)	0.45 ± 0.40 (n = 74)	0.02	0.68 ± 0.80 (n = 22)	0.81	0.07
	3 months	0.49 ± 0.42 (n = 116)	0.47 ± 0.43 (n = 89)	0.30	0.53 ± 0.40 (n = 27)	0.55	0.53
	6 months	0.55 ± 0.54 (n = 100)	0.48 ± 0.43 (n = 75)	0.21	0.76 ± 0.78 (n = 25)	0.06	0.02
	12 months	0.60 ± 0.64 (n = 67)	0.56 ± 0.53 (n = 40)	0.52	0.66 ± 0.79 (n = 27)	0.36	0.54
	Last FU	0.55 ± 0.57 (n = 129)	0.49 ± 0.42 (n = 98)	0.58	0.74 ± 0.86 (n = 31)	0.09	0.03
Continued							

Indication/outcome	Timepoint	Total	Amelivu	P-value	LucenBS	P-value	P-value†
CMT (µm)	Baseline	444.20 ± 151.98 (n = 128)	458.00 ± 153.82 (n = 99)	–	397.07 ± 137.78 (n = 29)	–	0.06
	1 month	377.21 ± 131.88 (n = 92)	373.34 ± 133.85 (n = 73)	< 0.01	392.05 ± 126.40 (n = 19)	0.81	0.59
	3 months	381.26 ± 144.93 (n = 113)	373.54 ± 143.07 (n = 89)	< 0.01	409.88 ± 151.28 (n = 24)	0.55	0.28
	6 months	392.36 ± 146.49 (n = 96)	382.93 ± 146.41 (n = 76)	< 0.01	428.20 ± 144.85 (n = 20)	0.06	0.22
	12 months	365.48 ± 148.14 (n = 64)	374.20 ± 167.22 (n = 40)	< 0.01	350.96 ± 111.09 (n = 24)	0.36	0.55
	Last FU	382.55 ± 158.02 (n = 125)	392.42 ± 165.41 (n = 101)	< 0.01	341.04 ± 115.95 (n = 24)	0.09	0.15

**Table 3.** Visual and anatomical outcomes by indication and ranibizumab biosimilar type. Data are presented as mean ± standard deviation with number of available cases for each timepoint. AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CMT, central macular thickness; DME, diabetic macular edema; LogMAR, logarithm of the minimum angle of resolution; RVO ME, retinal vein occlusion macular edema. P-values were calculated using paired t-test comparing each timepoint to baseline. †Inter-group p-value was calculated using independent t-test for Amelivu and LucenBS comparison. Direct comparison between two biosimilars should be interpreted with caution due to baseline differences in patient demographics, treatment history, and disease severity, which reflect institutional practice patterns rather than comparative drug efficacy. N = number of available cases for each timepoint.



**Fig. 2.** Best-corrected visual acuity (BCVA) and central macular thickness changes (CMT) over time by indication and ranibizumab biosimilar type. (A) BCVA changes shown in logarithm of the minimum angle of resolution (logMAR) units. (B) CMT changes shown in micrometers (µm). Data are presented as mean ± standard error of the mean (SEM). BCVA, best-corrected visual acuity; DME, diabetic macular edema; FU, follow-up; logMAR, logarithm of the minimum angle of resolution; RVO ME, retinal vein occlusion macular edema. \*P < 0.05 comparing Amelivu and LucenBS groups using independent t-test at each timepoint.

anatomical responses, and anti drug antibody (ADA) rates compared to reference<sup>11</sup>. The recent QL1205 program likewise demonstrated clinical equivalence under monthly dosing<sup>12</sup>. Collectively, our effectiveness and safety results under pragmatic T&E/PRN care are directionally consistent with these trials while reflecting the lower injection intensity typical of routine practice.

Our findings align with and extend the growing body of international evidence supporting ranibizumab biosimilar efficacy and safety. Several studies from India have evaluated India-specific biosimilars (Razumab, Ranizurel, Ranieyes) in real-world settings, demonstrating comparable efficacy to reference ranibizumab<sup>19–21</sup>. Recent studies from Japan and Korea have also reported favorable outcomes with ranibizumab biosimilars (BS1 and CKD-701) in various retinal diseases including AMD, RVO, and DME<sup>22–24</sup>. However, our study makes several unique contributions to this literature. First, unlike India-specific biosimilars, Amelivu is an EMA/FDA/MFDS-approved biosimilar, providing greater regulatory assurance and global applicability. Second, our study encompasses a broader range of retinal diseases beyond nAMD, including RVO, DME, and myopic CNV, demonstrating consistent efficacy across multiple indications. Third, with over 1,000 eyes and 6-month follow-up, our study provides one of the largest real-world datasets for ranibizumab biosimilars in Asian populations.

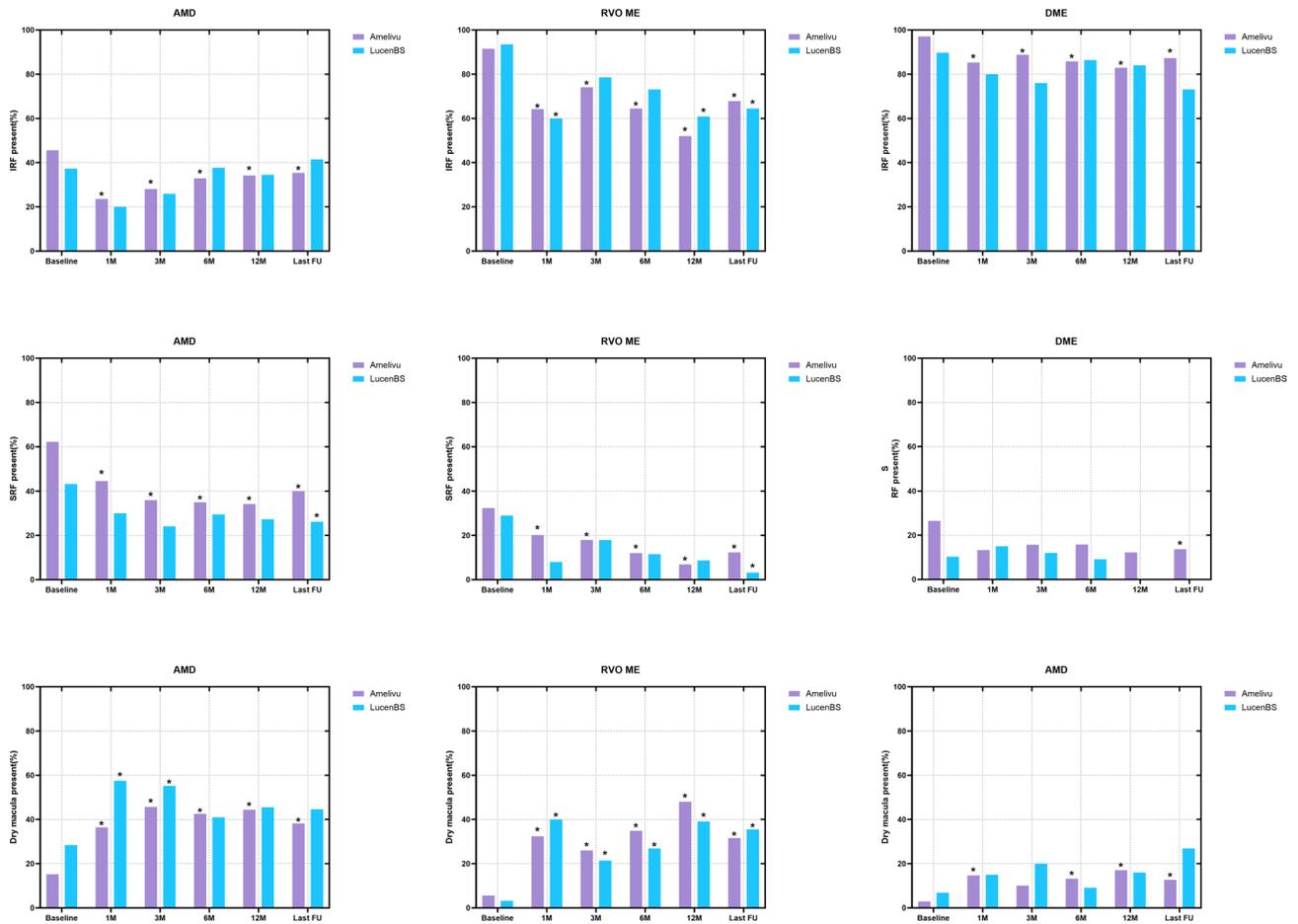
In nAMD, our cohort exhibited sustained anatomical improvement and maintenance or improvement in BCVA consistent with originator ranibizumab benchmarks from the MARINA/ANCHOR study<sup>2–4</sup> and modern biosimilar trials<sup>10,12,18</sup>. Real-world dosing schedules in our cohort differ from the fixed monthly regimens used in historical RCTs, which likely explains smaller absolute visual gains despite robust drying. The pattern of early fluid resolution followed by stabilization mirrors prior experience with originator ranibizumab under PRN

Treatment history/outcome	Timepoint	Total	Amelivu	p-value	LucenBS	p-value	P-value†
Treatment naïve							
BCVA (LogMAR)	Baseline	0.55 ± 0.56 (n = 408)	0.56 ± 0.57 (n = 370)	–	0.44 ± 0.45 (n = 38)	–	0.223
	1 month	0.47 ± 0.50 (n = 363)	0.47 ± 0.51 (n = 331)	< 0.01	0.46 ± 0.49 (n = 32)	0.48	0.894
	3 months	0.45 ± 0.52 (n = 370)	0.45 ± 0.52 (n = 338)	< 0.01	0.53 ± 0.55 (n = 32)	0.50	0.392
	6 months	0.38 ± 0.43 (n = 324)	0.38 ± 0.43 (n = 296)	< 0.01	0.43 ± 0.39 (n = 28)	0.47	0.522
	12 months	0.38 ± 0.45 (n = 215)	0.39 ± 0.46 (n = 190)	< 0.01	0.36 ± 0.37 (n = 25)	0.70	0.740
	Last FU	0.50 ± 0.58 (n = 321)	0.50 ± 0.57 (n = 284)	< 0.01	0.50 ± 0.61 (n = 37)	0.54	0.995
CMT (µm)	Baseline	421.39 ± 202.92 (n = 396)	422.31 ± 201.64 (n = 359)	–	412.43 ± 217.64 (n = 37)	–	0.778
	1 month	313.05 ± 150.26 (n = 363)	315.41 ± 151.06 (n = 332)	< 0.01	287.74 ± 141.18 (n = 31)	< 0.01	0.328
	3 months	313.29 ± 132.01 (n = 358)	311.01 ± 121.83 (n = 329)	< 0.01	339.10 ± 218.11 (n = 29)	0.02	0.273
	6 months	312.62 ± 130.62 (n = 317)	315.78 ± 132.45 (n = 291)	< 0.01	277.23 ± 103.63 (n = 26)	< 0.01	0.150
	12 months	309.60 ± 138.93 (n = 212)	310.59 ± 136.87 (n = 187)	< 0.01	302.20 ± 156.38 (n = 25)	0.01	0.777
	Last FU	318.39 ± 128.04 (n = 394)	320.97 ± 127.78 (n = 360)	< 0.01	291.06 ± 129.49 (n = 34)	< 0.01	0.193
Previously treated							
BCVA (LogMAR)	Baseline	0.68 ± 0.65 (n = 742)	0.68 ± 0.64 (n = 634)	–	0.71 ± 0.67 (n = 108)	–	0.639
	1 month	0.63 ± 0.65 (n = 547)	0.62 ± 0.64 (n = 473)	< 0.01	0.71 ± 0.72 (n = 74)	0.66	0.227
	3 months	0.61 ± 0.61 (n = 656)	0.61 ± 0.62 (n = 558)	< 0.01	0.63 ± 0.56 (n = 98)	0.14	0.798
	6 months	0.65 ± 0.64 (n = 555)	0.63 ± 0.63 (n = 458)	< 0.01	0.74 ± 0.70 (n = 97)	0.93	0.131
	12 months	0.67 ± 0.69 (n = 370)	0.66 ± 0.67 (n = 277)	0.23	0.71 ± 0.73 (n = 93)	0.34	0.532
	Last FU	0.71 ± 0.68 (n = 614)	0.71 ± 0.68 (n = 507)	0.80	0.69 ± 0.69 (n = 107)	0.68	0.808
CMT (µm)	Baseline	379.08 ± 146.36 (n = 710)	383.53 ± 145.25 (n = 606)	–	353.12 ± 150.79 (n = 104)	–	<b>0.050</b>
	1 month	353.81 ± 147.82 (n = 517)	355.07 ± 147.45 (n = 452)	< 0.01	345.06 ± 151.23 (n = 65)	< 0.01	0.610
	3 months	340.19 ± 132.54 (n = 625)	344.14 ± 131.60 (n = 532)	< 0.01	317.57 ± 136.38 (n = 93)	0.01	0.074
	6 months	341.19 ± 132.09 (n = 532)	341.06 ± 125.35 (n = 441)	< 0.01	341.80 ± 161.64 (n = 91)	0.31	0.961
	12 months	325.62 ± 127.47 (n = 355)	331.71 ± 122.25 (n = 267)	< 0.01	307.14 ± 141.29 (n = 88)	< 0.01	0.117
	Last FU	341.96 ± 141.76 (n = 708)	346.56 ± 141.86 (n = 609)	< 0.01	313.69 ± 138.47 (n = 99)	< 0.01	<b>0.032</b>

**Table 4.** Visual and anatomical outcomes by treatment history and ranibizumab biosimilar type. Data are presented as mean ± standard deviation with number of available cases for each timepoint. Treatment naïve patients had no prior anti-VEGF injections; previously treated patients had received anti-VEGF injections before ranibizumab biosimilar treatment. BCVA, best-corrected visual acuity; CMT, central macular thickness; FU, follow-up; LogMAR, logarithm of the minimum angle of resolution. P-values were calculated using paired t-test comparing each timepoint to baseline. †Inter-group p-value for comparison between Amelivu and LucenBS groups (independent t-test). Direct comparison between two biosimilars should be interpreted with caution due to baseline differences in patient demographics, treatment history, and disease severity, which reflect institutional practice patterns rather than comparative drug efficacy.

and T&E strategies, suggesting that biosimilar agents function similarly in suppressing VEGF-driven exudation in choroidal neovascularization<sup>15,25</sup>. For DME and RVO-ME, we observed consistent CMT reduction with progressive OCT fluid resolution and increasing “dry macula” rates. RVO ME demonstrated more pronounced visual and anatomical responses, consistent with the acute vascular nature of retinal vein occlusions where prompt anti-VEGF intervention can effectively address the primary pathophysiologic driver<sup>26</sup>. These findings underscore the importance of early intervention in RVO-ME and support the continued prioritization of anti-VEGF therapy as first-line treatment for this indication. In DME, the limited visual gains despite significant anatomical improvements align with the chronic, metabolic nature of diabetic retinopathy, where sustained VEGF elevation and ongoing inflammatory processes may limit functional recovery even after successful fluid resolution<sup>27</sup>. The role of concurrent systemic factors, including glycemic control, blood pressure management, and diabetic nephropathy, likely contribute to the ceiling effect on visual outcomes, emphasizing that anti-VEGF therapy, while effective for anatomical improvements, represents only one component of comprehensive diabetic eye care. Furthermore, in our cohort, eyes with DME presented with relatively better baseline logMAR VA compared with those with neovascular AMD or RVO, while central macular thickness remained increased (Table 2). This pattern is consistent with a potential ceiling effect, which may have limited the magnitude of visual gain despite clear anatomical improvement.

Treatment-naïve eyes tended to show greater early gains than previously treated eyes, consistent with expectations based on disease chronicity and prior exposure. This pattern aligns with our previous Korean real-world evidence, which reported that treatment-naïve patients achieved superior visual outcomes (7.5 vs 4 letters) and higher rate of ≥ 3-line improvement (30.2% vs 21.1%) with originator ranibizumab<sup>28</sup>. Among previously treated eyes, we did not detect safety concerns or signals of diminished effectiveness following transition to a biosimilar, concordant with trial-level immunogenicity analyses showing no clinically meaningful ADA impact on efficacy, safety, or pharmacokinetics<sup>9</sup>. While non-medical switching and attribution bias cannot be formally



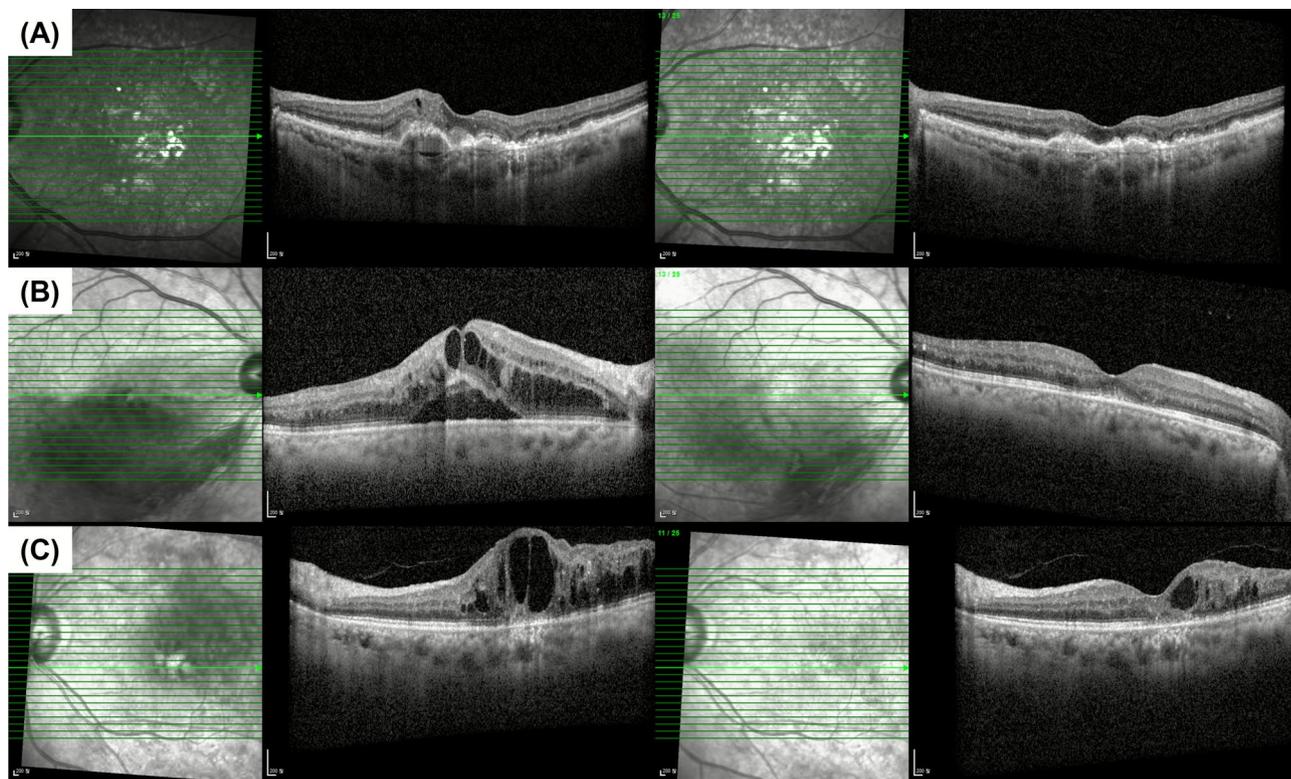
**Fig. 3.** Optical coherence tomography fluid changes by indication and ranibizumab biosimilar type. Upper panels show intraretinal fluid (IRF) presence, middle panels show subretinal fluid (SRF) presence, and lower panels show dry macula achievement. DME, diabetic macular edema; FU, follow-up; RVO ME, retinal vein occlusion macular edema. \*P < 0.05 compared to baseline using chi-square test or Fisher’s exact test when expected frequency < 5.

assessed without patient-reported outcomes, the stability of functional and anatomical metrics argue against a negative switch effect.

Regarding the duration of action, recent evidence suggests that ranibizumab biosimilars is comparable to that of reference ranibizumab. Phase 3 trials of FYB201 and SB11, which used fixed monthly dosing in patients with no prior treatment for nAMD, demonstrated nearly identical outcomes in terms of best-corrected visual acuity and OCT-based retinal thickness between the biosimilar and reference groups for 48–52 weeks. There were no relevant differences in retreatment patterns, cumulative injection exposure or safety signals<sup>10,15</sup>. Similarly, a phase 3 trial in Korea employing a regimen closer to routine practice (three monthly loading doses followed by PRN retreatment) reported comparable visual and anatomical outcomes, with a virtually identical mean number of injections over 12 months for CKD-701 and reference ranibizumab.<sup>11</sup> Real-world studies of reference ranibizumab, including global and Korean cohorts from the LUMINOUS program, further show that most patients receive approximately 4–6 injections during the first treatment year and that higher injection frequency, rather than intrinsic differences in nominal duration of action, is the major determinant of visual gain<sup>29,30</sup>. In this context, the visual and anatomical stability observed in our cohort with Amelivu and LucenBS under T&E/PRN regimens, together with the absence of any systematic signal of earlier recurrence or excess switching because of perceived loss of effect, suggests that these two ranibizumab biosimilars have a comparable functional duration of action to previously reported ranibizumab biosimilars and the original molecule.

Although some time points favored Amelivu in visual outcomes, these differences should be interpreted cautiously. Previous RCTs have established that ranibizumab biosimilars are equivalent to the reference product<sup>11,15,18</sup>. LucenBS use was concentrated in fewer centers and in a smaller, older, and more heavily pretreated case-mix, amplifying confounding by indication. From a clinical perspective, both agents appear suitable for initiating or continuing therapy. The choice between them would be more influenced by factors such as availability, cost, and institutional policy than by anticipated differences in clinical response.

Across the cohort, ocular adverse events were infrequent, and we identified no new safety signals attributable to biosimilar use. Trial programs for FYB201, SB11, CKD-701, and QL1205 consistently report safety profiles



**Fig. 4.** Representative optical coherence tomography images showing treatment response to Amelivu across different indications. Optical coherence tomography (OCT) images demonstrating anatomical improvements following Amelivu (ranibizumab biosimilar) treatment across three major retinal diseases. Left panels show baseline OCT scans before treatment; right panels show OCT scans at 1 month after Amelivu injection. **(A)** Neovascular age-related macular degeneration showing resolution of subretinal and intraretinal fluid. **(B)** Retinal vein occlusion with macular edema demonstrating marked reduction in cystic spaces and central macular thickness. **(C)** Diabetic macular edema with notable improvement in retinal thickness and cystic changes. These cases illustrate the consistent anatomical response to ranibizumab biosimilar treatment across different disease etiologies.

comparable to reference ranibizumab with low ADA incidence and no clinically meaningful ADA-related impact on outcomes<sup>9–12,18</sup>. A recent systematic review and meta-analysis of ranibizumab biosimilars found no significant differences in treatment-emergent adverse events, serious adverse events, or specific ocular complications including endophthalmitis, retinal hemorrhage, or IOP-related events compared to reference ranibizumab<sup>31</sup>. While concerns about systemic vascular events have been raised for intravitreal anti-VEGF therapy, pooled evidence suggests no clear increase in major adverse cardiovascular events with ophthalmic dosing<sup>32</sup>. Our study was not powered for rare events, and longer follow-up is warranted. We observed standard rates of non-serious ocular events typical of intravitreal injection practice, with very low rates of infectious endophthalmitis consistent with large originator cohorts from the LUMINOUS study<sup>30,33</sup>.

This study has several limitations. The study design was retrospective, which may have resulted in residual confounding. Baseline imbalances and center effects were observed, such as the use of LucenBS, which was clustered at a few sites. The indications were found to be heterogeneous and visit intervals and OCT protocols varied. Additionally, missing data with possible informative censoring could have biased the estimates. Moreover, the study was not powered for formal non-inferiority testing between biosimilars, making between-biosimilar comparisons exploratory and hypothesis-generating. Because no prospective sample-size calculation was performed, our study may be underpowered to detect rare safety events or small differences between biosimilar agents. Moreover, as OCT parameters were measured and interpreted by retina specialists at each center without a centralized reading center, inter-observer agreement statistics were not available. Furthermore, as specific reasons for treatment switching were not consistently documented in medical records, the underlying rationale for switching could not be reliably determined in most cases. Despite these limitations, our study provides valuable real-world evidence through its large, multicenter design encompassing multiple labeled indications and including both treatment-naïve and previously treated eyes. The use of standardized outcome definitions facilitates meaningful comparison with trial literature while remaining in accordance with actual clinical practice patterns, providing insights that complement controlled trial environments.

In a large multicenter real-world cohort, ranibizumab biosimilars delivered effective and safe care across major retinal diseases in real world settings. These findings complement phase 3 equivalence trials and support broader biosimilar adoption to maintain adequate treatment intensity and access. The excellent safety profile observed,

with only one minor ocular adverse event across 1,153 eyes treated with 3,575 injections, provides reassuring real-world evidence for clinicians considering biosimilar adoption. Prospective confirmation, methodologically rigorous comparative-effectiveness research, and longer-term safety surveillance are warranted to optimize outcomes and sustain vision at the population level.

### Data availability

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

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### References

- Finger, R. P. et al. Anti-vascular endothelial growth factor in neovascular age-related macular degeneration—a systematic review of the impact of anti-VEGF on patient outcomes and healthcare systems. *BMC Ophthalmol.* **20**, 294 (2020).
- Waring, R. Ranibizumab for neovascular age-related macular degeneration. *N. Engl. J. Med.* **355**, 1419–1431 (2006).
- Brown, D. M. et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N. Engl. J. Med.* **355**, 1432–1444 (2006).
- Brown, D. M. et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* **116**, 57–65.e5 (2009).
- Varma, R. et al. Improved vision-related function after ranibizumab for macular edema after retinal vein occlusion: results from the BRAVO and CRUISE trials. *Ophthalmology* **119**, 2108–2118 (2012).
- Brown, D. M. et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology* **120**, 2013–2022 (2013).
- Kelkar, A. et al. Factors affecting compliance to intravitreal anti-vascular endothelial growth factor therapy in Indian patients with retinal vein occlusion, age-related macular degeneration, and diabetic macular edema. *Indian J. Ophthalmol.* **68**, 2143–2147 (2020).
- Hariprasad, S. M. et al. An introduction to biosimilars for the treatment of retinal diseases: a narrative review. *Ophthalmol. Ther.* **11**, 959–982 (2022).
- Bressler, N. M. et al. Immunogenicity with ranibizumab biosimilar SB11 (Byooviz) and reference product lucentis and association with efficacy, safety, and pharmacokinetics: a post hoc analysis of a phase 3 randomized clinical trial. *JAMA Ophthalmol.* **141**, 117–127 (2023).
- Holz, F. G. et al. Efficacy and safety of biosimilar FYB201 compared with ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* **129**, 54–63 (2022).
- Yoon, C. K. et al. Efficacy and safety of a new ranibizumab biosimilar CKD-701 using a pro re nata treatment regimen in neovascular age-related macular degeneration: A phase 3 randomized clinical trial. *PLoS ONE* **17**, e0275611 (2022).
- Hamouz, J. et al. Efficacy and safety of ranibizumab biosimilar QL1205 in neovascular age-related macular degeneration. *Ophthalmol. Retina* **9**, 343–351 (2025).
- Sharma, A. et al. Biosimilars for retinal diseases: an update. *Am. J. Ophthalmol.* **224**, 36–42 (2021).
- Lee, H., Sharma, A. & Woo, S. J. Clinical trials of aflibercept biosimilars: a review. *J. Ocul. Pharmacol. Ther.* <https://doi.org/10.1089/jop.2025.0040> (2025).
- Bressler, N. M. et al. Biosimilar SB11 versus reference ranibizumab in neovascular age-related macular degeneration: 1-year phase III randomised clinical trial outcomes. *Br. J. Ophthalmol.* **107**, 384–391 (2023).
- Ministry of Food and Drug Safety of the Republic of Korea. Amelivu [<https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCa che?cacheSeq=202202008%26updateTs=2023-02-15%2015:44:12.247591>] (Accessed 02 Sept 2025).
- Sharma, A. et al. Anti-VEGF biosimilars for retinal diseases survey 2023- India (Bio-INDAS) by the International Retina Biosimilar Study Group (Inter-BIOS Group) in collaboration with the Vitreo-Retinal Society of India (VRSI). *Eye* **38**, 3392–3395 (2024).
- Woo, S. J. et al. Efficacy and safety of a proposed ranibizumab biosimilar product vs a reference ranibizumab product for patients with neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol.* **139**, 68 (2021).
- Sharma, S., Khan, M. A. & Chaturvedi, A. Real-life clinical effectiveness of Razumab\* (the world's first biosimilar of ranibizumab) in retinal vein occlusion: a subgroup analysis of the pooled retrospective RE-ENACT study. *Ophthalmol. Int. J. Ophthalmol.* **241**, 24–31 (2018).
- Sharma, A. et al. Ranizurel safety evaluation in real-world -(RaSER) study. *Am. J. Ophthalmol. Case Rep.* **25**, 101358 (2022).
- Sharma, A. et al. Biosimilar ranibizumab (ranieyes) safety and efficacy in the real world: BRESER study. *J. Vitreoretin. Dis.* <https://doi.org/10.1177/24741264251322213> (2025).
- Ueda-Consolvo, T. et al. Biosimilar ranibizumab (BS1) – early experience from Japan (BRIJ study). *Eye* **38**, 3193–3196 (2024).
- Shin, D., Kim, Y. & Kim, J. H. Short-term outcomes of ranibizumab biosimilar CKD-701 treatment in macular edema secondary to retinal vein occlusion. *J. Korean Ophthalmol. Soc.* **66**, 27–35 (2025).
- Yoon, Y. S. & Kim, J. H. Short-term anatomical outcomes of switching from bevacizumab to the ranibizumab biosimilar CKD-701 in neovascular age-related macular degeneration. *J. Retina* **9**, 127–133 (2024).
- Loewenstein, A. et al. Randomized trial of biosimilar XSB-001 versus reference ranibizumab in patients with neovascular age-related macular degeneration. *Ophthalmol. Retina* **7**, 753–761 (2023).
- Campochiaro, P. A. et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* **117**, 1102–1112.e1 (2010).
- Diabetic Retinopathy Clinical Research Network. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology* **114**, 525–536 (2007).
- Woo, S. J., Cho, G. E. & Cho, J. H. Short-term efficacy and safety of ranibizumab for neovascular age-related macular degeneration in the real world: a post-marketing surveillance study. *Korean J. Ophthalmol. KJO* **33**, 150–166 (2019).
- Holz, F. G. et al. Ranibizumab treatment patterns in prior ranibizumab-treated neovascular age-related macular degeneration patients: Real-world outcomes from the LUMINOUS study. *PLoS ONE* **15**, e0244183 (2020).
- Sagong, M., Woo, S. J., Lee, Y., LUMINOUSTM study investigators from South Korea. Real-World effectiveness, treatment pattern, and safety of ranibizumab in Korean patients with neovascular age-related macular degeneration: subgroup analyses from the LUMINOUS study. *Clin. Ophthalmol. Auckl. NZ* **15**, 1995–2011 (2021).
- Hatamnejad, A., Dadak, R., Orr, S., Wykoff, C. & Choudhry, N. Systematic review of efficacy and meta-analysis of safety of ranibizumab biosimilars relative to reference ranibizumab anti-VEGF therapy for nAMD treatment. *BMJ Open Ophthalmol.* **8**, e001205 (2023).
- Ngo Ntjam, N. et al. Cardiovascular adverse events with intravitreal anti-vascular endothelial growth factor drugs: a systematic review and meta-analysis of randomized clinical trials. *JAMA Ophthalmol.* **139**, 1–11 (2021).

33. Holz, F. G. et al. Ranibizumab treatment in treatment-naive neovascular age-related macular degeneration: Results from luminous, a global real-world study. *Retina Phila. Pa* **40**, 1673–1685 (2020).

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## Declarations

### Competing interests

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### Additional information

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