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REVIEW

# Current biosimilar anti-VEGF drugs in retinal diseases

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**Abstract**

Anti-vascular endothelial growth factor (anti-VEGF) drug is a biological drug that is widely used in the treatment of retinal diseases and imposes a high financial burden on the healthcare system. The introduction of biosimilar drugs has come to the forefront with the expiration of patents on biological drugs. Biosimilar drugs have the same effectiveness and safety, but are more cost-effective. This feature of biosimilar drugs offers an important opportunity to reduce healthcare costs and to ensure patient compliance. This review aims to provide an overview of biosimilar drugs, highlight their advantages, and discuss both approved and investigational anti-VEGF biosimilar drugs. The goal was to provide ophthalmologists with a comprehensive understanding of this rapidly evolving field.

**Keywords:** Aflibercept biosimilar; Anti-VEGF; bevacizumab biosimilar; biosimilar; ranibizumab biosimilar.

With the development of biological agents targeting vascular endothelial growth factor (anti-VEGF), there has been great progress in treating retinal diseases.[1] The first anti-VEGF drug to emerge was bevacizumab (Avastin; Genentech), which was approved by the United States Food and Drug Administration (FDA) in 2004 for treating metastatic colon and rectal carcinoma. Bevacizumab has also been shown off-label to be effective in neovascular-type age-related macular degeneration (nAMD).[2] Pegaptanib (Macugen, Pfizer) was the first anti-VEGF drug approved by the FDA for the treatment of nAMD in 2004.[3] Subsequently, Ranibizumab (Lucentis; Genentech) in 2006 and aflibercept (Eylea; Regeneron) in 2011 were approved for intraocular use for the treatment of nAMD.[4] Over time, treatment indications for these drugs have expanded. Their use has begun in cases of diabetic retinopathy (DR), diabetic macular edema (DME), macular edema secondary to retinal vein occlusions, and myopic choroidal neovascularization.[5] Ranibizumab and aflibercept are the most widely used anti-VEGF agents approved for ophthalmic use in the United States (US) and the European Union (EU).[3] In 2020, ranibizumab, aflibercept, and bevacizumab were among the top ten drugs with the highest drug expenditures in Medicare Part B among all drug expenditures.[6] It is also stated that more than 3.5 billion dollars are spent annually by Medicare Part B on anti-VEGF drugs.[7]

In recent years, faricimab (Vabysmo; Genentech/Roche) and brolucizumab (Beovu, Novartis) have also been approved for ophthalmic use.[8] Faricimab is a drug with a bispecific effect that can block VEGF-A and angiopoietin 2. Its use in treatment is 6 mg intravitreal (IV) doses monthly for the

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first 4 months, and then, the same dose is applied 8 or 12 weeks later, depending on optical coherence tomography findings and visual acuity evaluations.[9] Brolucizumab, a single-chain humanized antibody fragment, is used in 6mg IV doses every 8–12 weeks after 3-month loading doses.[8] Although brolucizumab is an approved anti-VEGF agent, the emergence of various inflammatory side effects has limited its widespread use.[10] The duration of action of drug was up to 3–4 months.[11]

US patents for bevacizumab, ranibizumab, and aflibercept have expired in 2019, 2020, and 2023, respectively. European patents for bevacizumab and ranibizumab will die in 2022. Aflibercept's patent will expire in 2025.[12] The expiration of these patent protections has brought the use of biosimilar drugs, which are alternatives to biological drugs, into the agenda.

## Differences Between Biosimilar Drug and Generic Drug

Biosimilar drugs are molecules that have a pharmacokinetic, pharmacodynamic, immunogenicity, safety, and efficacy profile similar to that of the original biological drug. The definition of biosimilars differs from that of generic drugs. Generic drugs can be easily produced by completing chemical formulas and are stable. Biosimilars, on the other hand, require living cells during their production. The fact that these products are produced by different manufacturers using different cell lines and purified by different methods causes small differences with the reference product.[13,14] In addition, different living cells and the processes followed during the production phase may cause differences in the immunogenicity of biosimilars, and with this feature, they differ from the definition of a generic drug.[13]

## Production and Cost Advantages of Biosimilar Drugs

There has been an intense effort worldwide to produce biosimilars and make them available as soon as possible. The biggest reason for this is the costs and profit amounts of these drugs used.[13] The approval pathway for biosimilar drugs differs from that of the original biological drugs. Since biosimilars are similar to the original biological molecules, they do not require a discovery phase or a phase 2 phase, where the first effectiveness of these molecules on patients is observed. As a result, while the production of original biological drugs will take 10-15 years, the development process of biosimilars can be shortened to approximately 8 years.[13,15] In addition, heavy investment in clinical trials of biosimilars is not necessary. It is sufficient to conduct at least one clinical study comparing the pharmacokinetics of the original biological drug and biosimilars, and at least one randomized controlled study large enough to demonstrate equivalence. As a result, while 1200–2500 million US dollars are required for the development of original biological drugs, 100–200 million US dollars may be sufficient for the production of biosimilars.[13,16] The cost required to produce a biosimilar drug is significantly lower than that of the original biological drug. Considering that cost is an important step in medical decision making and drug selection in most countries, it seems inevitable that cheaper biosimilar drugs will come into use and become widespread. Another advantage is that patient compliance with treatment may be strengthened as a result of reduced drug costs. Increasing compliance with treatment may make it easier for healthcare services to yield successful results.[17] As a result, the extra financial burden imposed by non-compliance with treatment on the healthcare system can be eliminated.[18]

The aim of this article is to gain information about drugs that are biosimilars of anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept), which are thought to help ophthalmologists provide cost-effective treatment services in the coming years and to examine the latest developments on this subject.

## Ophthalmic Bevacizumab

The development of drugs biosimilar to bevacizumab, which is widely used off-label in nAMD, is of interest in the field of ophthalmology. Many biosimilars have been approved for the treatment of bevacizumab. Biosimilar drugs are frequently used to treat oncological diseases. Unlike other drugs, Outlook Therapeutics is working to demonstrate the efficacy of ONS-5010/ LYTENAVA™ (bevacizumab-vikg), an intraocular formulation of bevacizumab biosimilar, in patients with nAMD and other retinal diseases, and to be the first bevacizumab formulation approved by the FDA.[19,20] The NORSE TWO study evaluated whether the safety and efficacy of ONS-5010 (1.25 mg) administered monthly was superior to that of ranibizumab. In this evaluation, ranibizumab was administered using the PIER study protocol (3-monthly loading injections, then 0.5 mg fixed injection administered every 3 months), and these 12-month results were compared. They stated that 41.7% of ONS-5010 and 23.1% of ranibizumab achieved a gain of ≥15 best-corrected visual acuity (BCVA) letters in 12 months.[21]

In 2022, the FDA accepted the biologics license application for bevacizumab vikg (ONS-5010/Lytenava), an investigational ophthalmic formulation of bevacizumab. The FDA has set the target date as August 2023. This drug was the first officially labeled ophthalmic formulation of bevacizumab to enter the market. However, in 2023, the FDA found several problems with drug administration and did not approve of it. The FDA cited several chemistry, manufacturing, and control issues, observations from pre-approval manufacturing inspections, and most importantly, the need for more confirmatory clinical evidence. Approval of the intravitreal form of this drug will affect the off-label use of bevacizumab.[22]

## Bevacizumab Biosimilars

Bevacizumab (Avastin) was marketed in Turkey under the name Altuzan (Roche, Switzerland). A wide variety of bevacizumab biosimilars have been developed. Bevax (MabXience, Spain) is a bevacizumab biosimilar launched on the Turkish market by Abdi İbrahim pharmaceutical company.[23]

ABP215 Mvasi (bevacizumab-awwb) (Amgen, Thousand Oaks, CA, USA; Allergan, Dublin, Ireland) is the first FDA-approved biosimilar to bevacizumab. It received FDA and EMA approval in 2017.[24,25]

Zirabev (bevacizumab-bvzr) (Pfizer, USA) was the second bevacizumab biosimilar to receive FDA approval. It received FDA and EMA approvals in 2019.[24,25]

Alymsys (bevacizumab-maly) (Amneal Pharmaceuticals LLC, US) became the third bevacizumab biosimilar to receive FDA approval. It was approved by the FDA in 2022.[25]

Vegzelma (bevacizumab-adcd) (CELLTRION, Inc.) is the fourth bevacizumab biosimilar to receive FDA approval. Approved in September 2022.[25] Bevacizumab biosimilars are summarized in Table 1.

## Ranibizumab Biosimilars

Razumab (Intas Pharmaceuticals Ltd., India) is the first ranibizumab biosimilar approved and launched in India in 2015.[26] Inflammatory side effects were observed after razumab was. Post-injection inflammation was detected in ten percent of the patients who received injections of the first three series of razumab. Endotoxin levels were corrected by modifying the drug-production process. As a result of the necessary corrections, the rate of ocular inflammation decreased significantly.[27] After the ocular inflammation side effect was reported in 2019, various studies have been conducted to investigate its safety, effectiveness, and immunogenicity. In a retrospective study, a significant improvement was found in both groups compared to the initial BCVA, and it was stated that there were similar side effect profiles in both groups.[28]

R-TPR-024 Ranizurel (Reliance Life Sciences Pvt Ltd, India) is a biosimilar to ranibizumab that was approved in India in October 2020. In the randomized (2:1) controlled double-blind Phase 3 study, which included 160 nAMD patients, it was stated that the patients with <15 letters missing at the end of 24 weeks were 105 patients in the Ranizurel arm and 53 patients in the ranibizumab arm, and it was determined that there was no statistical difference. It has been stated that there is no difference in terms of efficacy, safety, and immunogenicity.[29]

**Table 1.** Bevacizumab Biosimilars and Approval Status

| Biosimilars | Approval status |
|---|---|
| BCD-021 (Biocad, Saint Petersburg, Russia) | Russian Regulatory Body 2015 |
| mAbxience (mAbxience, Madrid, Spain) | Argentina Regulatory Body 2016 |
| Cizumab (Hetero, Hyderabad, India) | DCGI 2016 |
| Bevacirel (Reliance Life Sciences, Mumbai, India) | DCGI 2016 |
| Krabeva (Biocon, Bangalore, India) | DCGI 2017 |
| Zybev (Zydus Cadila, Ahmedabad, India) | DCGI 2017 |
| Abevmy (Mylan Pharmaceuticals, South Africa) | DCGI 2017 |
| Bevatas (Intas, Ahmedabad, India) | DCGI 2017 |
| ABP215 Mvasi (Amgen, Thousand Oaks, CA, USA and Allergan, Dublin, Ireland) | FDA 2017, EMA 2017 |
| Zirabev (Pfizer, USA) | FDA 2019, EMA 2019 |
| Alymsys (bevacizumab-maly) (Amneal Pharmaceuticals LLC, US) | FDA 2022 |
| Vegzelma (bevacizumab-adcd) (CELLTRION, Inc.) | FDA 2022 |
| ONS-5010 Lytenava (Outlook Therapeutics, Inc) | Phase 3 completed |

DCGI: Drugs Controller General of India; FDA: Food and drug administration; EMA: European medicines agency.

SB11 Byooviz (Ranibizumab-nuna) (Samsung Bioepis, South Korea) was the first ranibizumab biosimilar to receive FDA approval in September 2021. The efficacy and safety of SB11 against ranibizumab were investigated in a phase 3 randomized double-blind multicenter study involving 705 patients with nAMD. They randomized the patients one-on-one and administered monthly injections of 0.5 mg SB11 or ranibizumab. The difference between SB11 and RBZ in BCVA from baseline at Week 52 was −0.6 letters (90% Confidence interval (CI) −2.1–0.9); the change in central subarea thickness compared to baseline was −14.9 µm (%95 CI, −25.3−−4.5). They found that serious adverse events that occurred during ocular treatment were 2.9% in the SB11 group and 2.3% in the ranibizumab group. As a result, they emphasized that SB11 is a ranibizumab biosimilar with similar efficacy, safety, pharmacokinetics, and immunogenicity to ranibizumab in the nAMD group.[30]

LUBT010 Ranieyes (Lupin Ltd., India) is biosimilar to Ranibizumab. Its effectiveness was evaluated in a prospective double-blind randomized phase 3 study in 19 countries, and it was approved in India. The study found that the rate of patients losing <15 letters from their BCVA score from baseline at 52 weeks was similar between the LUBT010 Ranieyes and ranibizumab groups. Furthermore, LUBT010 Ranieyes was found to have a positive safety and immunogenicity profile.[31]

Ranibizumab BS 1 (Senju Pharmaceutical Co., Ltd., in collaboration with Kids Well Bio Corporation, Japan) is a ranibizumab biosimilar that was approved for nAMD in Japan in September 2021. As a result of a Phase 3 clinical trial of ranibizumab BS in 176 patients and ranibizumab in 175 patients, it was stated that the BCVA of both groups was −1.5 letters (95% CI, −3.2–0.3) and showed equivalence in terms of safety.[32]

FYB-201 Cimerli (Ranibizumab-eqrn) (Formycon, Bioeq, Coherus Biosciences, Germany) was granted the title of the interchangeable product by the FDA for all indications of ranibizumab in August 2022.[33] COLUMBUS-AMD, a randomized (1:1) clinically controlled multicenter Phase 3 study, was studied in 477 patients to investigate the treatment of nAMD-related macular edema. At the end of the 48th week, it was stated that the change in BCVA compared to the baseline was +7.8±11.7 (median 8.0) in the FYB-201 group and 8.0±11.3 (median 8.0) in the ranibizumab group, and there was no statistical difference between both groups. They also stated that there was no current evidence of an increase in side effects. As a result, it was stated that it is biosimilar to ranibizumab in terms of clinical efficacy and safety in the treatment of nAMD.[34]

CKD-701 (Chong Kun Dang Pharmaceutical, South Korea) is a biosimilar of ranibizumab approved by the South Korean Ministry of Food and Drug Safety, pending approval from the United States.[33,35] To demonstrate the biosimilarity of CKD-701 with ranibizumab, a randomized (1:1) controlled double-blind phase 3 clinical study was designed, including 312 patients with nAMD and subfoveal choroidal neovascular membrane (CNVM). At the end of the 12th month, it was stated that the patients with <15 letters missing compared to the beginning were 128 patients and 132 patients in the CKD-701 and ranibizumab groups, respectively, and it was stated that there was no statistical difference between the two groups. It has also been stated that their safety and immunogenicity are not different and that they are biosimilar to ranibizumab.[36]

XSB-001 Ximluci (STADA Arzneimittel AG,Almanya and Xbrane Biopharma, Sweden) is a ranibizumab biosimilar approved by the EMA in November 2022 and pending FDA approval.[37] A total of 582 patients with active subfoveal CNVM were examined in a multicenter, double-blind, and randomized (1:1) Phase 3 study investigating the biosimilarity of XSB-001 and ranibizumab. At the end of 52 weeks, the mean least-squares (LS) was 6.4 letters in the XSB-001 group and 7.8 letters in the ranibizumab group (95% CI, −3.6–0.7) compared to the beginning. It was also emphasized that there was no clinical difference in anatomical safety and immunogenicity.[38]

Xlucane (Xbrane Biopharma, Sweden) is a biosimilar whose biosimilarity to ranibizumab was examined in the phase 3 XPLORE study in 580 participants with nAMD. At the end of 8 weeks, BCVA showed an effect similar to that of the original biologic. In addition, it was stated that no difference was detected regarding pharmacokinetics, safety, and immunogenicity.[39] It is awaiting approval in the US. Ranibizumab biosimilars are summarized in Table 2.

## Aflibercept Biosimilars

YESAFILI (Biocon Pharmaceuticals, India) (known as MYL1701P) is the first drug to be granted marketing authorization in the EU by the European Commission as a biosimilar to aflibercept. The effectiveness of the drug was tested in patients with DME in a double-blind and randomized multicenter study. The work was completed in September 2021.[40]

**Table 2.** Ranibizumab biosimilars and approval status

| Biosimilars | Approval status |
|---|---|
| Razumab (Intas Pharmaceuticals Ltd., India) | DCGI 2015 |
| R-TPR-024 Ranizurel (Reliance Life Sciences, India) | DCGI 2020 |
| SB11 Byooviz (Ranibizumab-nuna) (Samsung Bioepis, South Korea) | FDA 2021, EMA 2021 |
| LUBT010 Ranieyes (Lupin Ltd., India) | DCGI 2021 |
| Ranibizumab BS 1 (Senju Pharmaceutical Co., Ltd, in collaboration with Kids well Bio Corporation, Japan) | Japan Ministry of Health, Labour and Welfare 2021 |
| FYB-201 Cimerli (Ranibizumab-eqrn) (Formycon, Bioeq, Coherus Biosciences, Germany) | FDA 2022, EMA 2022 |
| CKD-701 (Chong Kun Dang Pharmaceutical, South Korea) | Ministry of Food and Drug Safety of Korea 2022 |
| XSB-001 Ximluci (STADA Arzneimittel AG, Germany and Xbrane Biopharma, Sweden ) | EMA 2022 |
| Xlucane (Xbrane Biopharma, Sweden) | Phase 3 completed |

DCGI: Drugs Controller General of India; FDA: Food and drug administration; EMA: European medicines agency.

FYB203 (Formycon AG/Klinge Biopharma GmBH, Germany) biosimilar efficacy was tested in nYBMD patients in a Phase 3 clinical randomized double-blind multicenter study called MAGELLAN-AMD.[41] The study was completed and the FDA accepted the abbreviated biological license application (aBLA) for review.[42]

CT-P42 (Celltrion, USA) biosimilar efficacy was investigated in patients with DME in a randomized controlled double-blind phase 3 clinical trial. The work was completed in 2023.[43] They have filed aBLA with the FDA for approved indications in non-pediatric patients.[42]

SB15 (Samsung Bioepis, South Korea) biosimilarity was tested in a randomized controlled double-blind multicenter Phase 3 clinical trial involving 449 patients with nAMD. At the end of 32 weeks, it was stated that the change in BCVA compared to the baseline in the SB15 and aflibercept groups was 7.6 (0.8) and 6.5 (0.8) (95% CI -0.9 to 3.1) letters, respectively. As a result, it was stated that it exhibited equivalent efficacy, safety, immunogenicity, and pharmacokinetic properties.[44,45] It is awaiting approval in the US.[33]

ABP 938 (Amgen, United States) was tested for biosimilarity to aflibercept in a randomized controlled double-blind multicenter Phase 3 clinical trial in 566 patients with nAMD. The study has been completed, but detailed data are not currently available.[46]

SCD411 (Sam Chun Dang Pharmaceuticals) was stated to be non-inferior to aflibercept based on the final results of the Phase 3 trial.[35] Sam Chun Dang Pharmaceuticals has entered into a licensing agreement with the Canadian company Apotex to supply SCD411.[47]

SOK583A1 (HEXAL; Sandoz, United States) was tested for its biosimilar activity to that of aflibercept in patients with nYBMD in the MYLIGHT study. Sandoz announced that it received positive results in this study. Detailed data are not currently available.[48]

AVT06 (Alvotech Swiss AG) is a biosimilar candidate whose biosimilarity to aflibercept has been tested in patients with nAMD, and whose phase 3 clinical trial is ongoing.[49]

ALT-L9 (Alteogen, South Korea) was tested for biosimilarity in a phase 3 study. The study is expected to be completed in early 2024 and receive approval in the first half of 2025.[35]

OT-702 (Ocumension Therapeutics (BA9101)/Shandong Boan Biological Technology, China) has been reported to have completed patient enrollment in the planned phase 3 study to compare its effectiveness and safety.[50] Aflibercept biosimilars are summarized in Table 3.

## Conclusion

As the patent protection for anti-VEGF drugs used in the treatment of retinal diseases expires and biosimilars of these agents are approved for clinical use, it is possible that biosimilars will gain a large share in the ophthalmology market. Considering the high cost of biological drugs and the rapidly increasing cost of healthcare services, the introduction of more economical biosimilars may be a pioneer in alleviating this heavy burden on healthcare services. Educational activities for ophthalmologists and increasing their awareness of biosimilar products will help physicians make decisions that can alleviate this economic burden on the healthcare system in drug selection. In addition, reducing patients' payment for biological drugs may increase patient compliance with treatment and positively affect visual prognosis.

**Table 3.** Aflibercept Biosimilars and Approval Status

| Biosimilars | Approval status |
|---|---|
| MYL1701P Yesafılı (Biocon Pharmaceuticals, India) | Marketing authorization in the EU by the European Commission 2023 |
| FYB203 (Formycon AG/Klinge Biopharma GmBH, Germany) | FDA accepted the aBLA |
| CT-P42 (Celltrion, USA) | Phase 3 completed |
| SB15 (Samsung Bioepis, South Korea) | Phase 3 completed |
| ABP 938 (Amgen, United States) | Phase 3 completed |
| SCD411 (Sam Chun Dang Pharmaceuticals) | Phase 3 completed |
| SOK583A1 (HEXAL; Sandoz, United States) | Phase 3 completed |
| AVT06 (Alvotech, Swiss AG) | Phase 3 active |
| ALT-L9 (Alteogen, South Korea) | Phase 3 active |
| OT-702 (Ocumension Therapeutics/Shandong Boan Biological Technology, China) | Phase 3 active |

aBLA: abbreviated biological license application; EU: European Union; FDA: Food and drug administration.

**Peer-review:** Externally peer-reviewed.

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