

## ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR BIOSIMILARS IN OPHTHALMOLOGY

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**Background/Purpose:** Anti-vascular endothelial growth factor therapies have proven effective in treating retinal diseases but come with a high financial burden to the patient and health care system. Biosimilar drugs present an opportunity to decrease the cost of these important ophthalmic medications, and several ophthalmic biosimilars are expected to be approved and enter the market in the coming years. The objectives of this review are to educate ophthalmologists on the safety and efficacy of biosimilars in ophthalmology in the United States and European Union, review the biosimilar manufacturing and approval process, and describe the upcoming ophthalmic biosimilars.

**Results:** Two ranibizumab biosimilars are currently approved in the United States and European Union. Additional ranibizumab biosimilars, as well as biosimilars for aflibercept and bevacizumab, are currently in clinical development.

**Conclusion:** Biosimilar use in ophthalmology is expected to grow with the patent expiration of two major anti-vascular endothelial growth factor drugs, ranibizumab and aflibercept, and the development of an ophthalmology-specific bevacizumab biosimilar. Financial savings from biosimilar use in ophthalmology have the potential to reduce economic burden, increase treatment adherence, and ultimately improve health outcomes.

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Anti-vascular endothelial growth factor (anti-VEGF) therapies, which target vascular permeability, angiogenesis, and inflammatory responses by inhibiting VEGF signaling, are standard-of-care treatments for patients with neovascular age-related macular degeneration (nAMD), macular edema after retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), and diabetic macular edema (DME).<sup>1</sup> Anti-VEGF therapies can also be used to improve diabetic retinopathy (DR) severity scores and for the treatment of patients with advanced DR, such as neovascularization in proliferative DR or vitreous hemorrhage secondary to proliferative DR.<sup>1</sup> Currently, ranibizumab (Lucentis; Genentech) and aflibercept (Eylea; Regeneron Pharmaceuticals) are the most commonly used anti-VEGF therapeutics approved for ophthalmic use in the United States and European Union (EU; Table 1).<sup>1</sup> Pegaptanib sodium (Macugen; Bausch + Lomb), the first VEGF-targeting agent approved by the U.S. Food and Drug Administration (FDA), is no longer commonly prescribed.<sup>1</sup> Recently, faricimab (Vabysmo; Genentech/Roche) and

brolicizumab (Beovu, Novartis) were also approved for ophthalmic use.<sup>2,3</sup>

Ranibizumab is a humanized, monoclonal, antigen-binding, anti-VEGF fragment administered by intravitreal injection (IVI) at a dose of 0.3 to 0.5 mg monthly.<sup>4</sup> Aflibercept, a VEGF-Trap fusion protein generated by fusing a human immunoglobulin G Fc fragment with key VEGF receptor domains, is administered at a dose of 2 mg by IVI every month for the first 3 months followed by 2 mg IVI every 2 months or more often if recommended by the treating physician.<sup>5</sup> Brolicizumab is a humanized, single-chain, antibody fragment administered by IVI at a dose of 6 mg every 8 to 12 weeks after three-monthly loading doses.<sup>3</sup> Although brolicizumab is an approved anti-VEGF agent, inflammatory side effects have limited its use.<sup>6</sup> Faricimab, a bispecific antibody that blocks VEGF-A and angiopoietin 2, is administered by IVI at a dose of 6.0 mg every month for the first 4 months then up to every 16 weeks per physician recommendation based on treatment response.<sup>2</sup>

Table 1. Commonly Used Anti-VEGF Originator Biologics Approved in the EU and United States

Molecule	Brand Name	EU Indications	U.S. Indications
Ranibizumab	Lucentis (Genentech)	nAMD, DR, DME, RVO, mCNV, other rare CNV, BRVO, and CRVO	nAMD, DR, DME, RVO, and mCNV
Aflibercept	Eylea (Regeneron Pharmaceuticals)	nAMD, DME, mCNV, CRVO, and BRVO	nAMD, RVO, DR, and DME
Brolucizumab	Beovu (Novartis)	nAMD	nAMD
Faricimab	Vabysmo (Genentech/Roche)	Under consideration for nAMD and DME	nAMD and DME

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CNV, choroidal neovascularization.

Bevacizumab (Avastin; Genentech), an anti-VEGF approved for oncology indications, is commonly used off-label as a compounded drug to treat retinal diseases in clinical practice.<sup>1</sup> Bevacizumab is the first-line treatment for patients with nAMD in many countries and is also commonly used in the United States.<sup>7</sup>

Because of the high cost of originator biologics, these approved therapies can result in significant financial burden that may affect treatment access. In health care systems without reimbursement, this burden falls to the patient and can result in treatment discontinuation or reduced adherence to the treatment regimen, ultimately leading to worse visual outcomes.<sup>8</sup> In health care systems with reimbursement, the sustainability of the health care system can be negatively affected by the financial burden of high treatment costs.

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Biosimilar drugs present an opportunity to decrease this financial burden because biosimilars are available at a lower cost than the originator products. Although prevalent in oncology, biosimilar use in ophthalmology is still in its infancy. As of September 2022, only two ranibizumab biosimilars are approved in the United States and EU,<sup>9,10</sup> but additional biosimilars are in development. This article aims to educate ophthalmologists on the safety and efficacy of biosimilars, increase awareness of the biosimilar approval process, and present the current and upcoming biosimilars in ophthalmology in the United States and EU.

## Overview of Biosimilars

In contrast to generic small-molecule medications, which are produced using well-defined chemical synthesis processes, biologics are produced in living systems.<sup>11</sup> Because of the complexity of biologics and the manufacturing process in biologic systems that can result in heterogeneous products, all biologics, including reference products, have small batch-to-batch differences because of slight variations in manufacturing.<sup>11</sup> Biosimilars produced by a different manufacturer are, therefore, not identical to the reference product but have been shown to be highly similar in structure and function to their reference biologic.<sup>11</sup> Biosimilars are not the same as generic small molecule drugs because generics are required to have the identical molecular ingredient as the reference product.<sup>11</sup>

Biosimilars undergo an extensive review and approval process to determine that there are no clinically meaningful differences between the biosimilar and reference product.<sup>12</sup> As less time and fewer resources are required for their development, approved biosimilars are additional, lower-cost treatment options for physicians and patients who also create a competitive market, potentially resulting in the reduction or stabilization of the price of the reference biologic.

It is important to note that biosimilars are not automatically interchangeable with the reference

product, but interchangeable status can be granted after presentation of additional evidence from clinical studies evaluating multiple switches between biosimilar and originator.<sup>11</sup> In addition, attaining interchangeable status varies depending on the country and/or state.<sup>11,13</sup>

### Biosimilar Approval Process

In the EU, the European Medicines Agency created biosimilar approval guidelines in 2005,<sup>14</sup> whereas the United States established safety and bioequivalence standards for biosimilars in 2009.<sup>12</sup> In the EU, these guidelines state that a biosimilar must demonstrate “similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise.”<sup>14</sup> For a biosimilar to be approved in the United States, the FDA requires evidence that there are “no clinically meaningful differences in safety, purity, and potency between the biosimilar and reference product.”<sup>12</sup>

In the United States and EU, biosimilarity is demonstrated using a stepwise approach,<sup>12,14</sup> which differs from the drug approval pathway for new originator biologics because of the greater focus on analytical data in the biosimilar pathway (Figure 1). Analytical and functional analyses must be performed to establish similarity in physicochemical properties, and preclinical studies can be performed to assess toxicity.<sup>12</sup> Clinical pharmacology studies evaluating pharmacokinetic similarity are a core determinant of biosimilarity, although pharmacodynamic and pharmacometric analyses can also be used.<sup>11</sup> The safety of the biosimilar candidate must be demonstrated to be similar to the reference product, and immunogenicity should be assessed when the reference product is known to have immune-mediated toxicity or safety consequences. Efficacy of a biosimilar product is assessed by determining whether selected clinical endpoints are within a predetermined equivalence margin.<sup>12</sup>

The totality of analytical, preclinical, pharmacokinetic, safety, and efficacy evidence, which is often obtained from more than one clinical study, is assessed by regulatory authorities before approving a biosimilar candidate.<sup>11</sup> If no clinically meaningful differences are found, the biosimilar can be approved for all indications of the reference biologic, even if the biosimilar was not directly studied in comparative clinical trials for these indications.<sup>12</sup> This regulatory principle, referred to as “indication extrapolation,” reduces the need for duplicative studies and contributes to the lower development costs of biosimilars.<sup>12</sup>

Once a biosimilar is approved, the naming of the biosimilar differs between the EU and United States; in the EU, the biosimilar is referred to by a unique

brand name paired with the international nonproprietary name (e.g., Byooviz [ranibizumab]).<sup>13</sup> In the United States, a unique nonproprietary biosimilar name is created by attaching a random, distinguishing, meaningless, 4-letter lowercase suffix by hyphen to the core drug name (e.g., ranibizumab-nuna).<sup>15</sup>

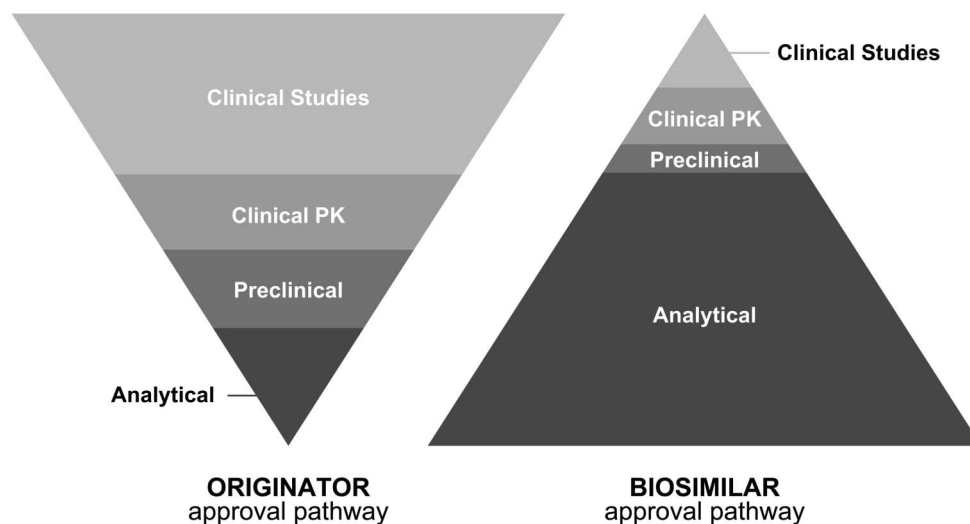
### Challenges in Biosimilar Use and Uptake

Given their new entry into the ophthalmology market, biosimilars may be met with a degree of hesitation by some health care providers and patients. In contrast with new biologics, the comparison of biosimilars to their reference product is based on a high degree of analytical similarity across a broad panel of orthogonal methods. Although longer-term real-world data are not available for biosimilars, the approval of a biosimilar depends on the totality of data and requires a highly similar safety profile to the reference biologic.<sup>12,14</sup> As with reference biologics after their initial approval, postmarketing pharmacovigilance is important to ensure that any rare adverse events (not detected in a clinical trial) are not missed. Similarly, batch-to-batch variations inherent to any biologic’s manufacturing may occur in biosimilars as they do in reference biologics, highlighting the need for monitoring of critical quality attributes in the manufacturing process.<sup>16,17</sup> In the oncology space, where biosimilars of growth factors and antibody products have been available for several years, approved biosimilars are accepted alternative product options in many settings. However, a recent white paper by the U.S. National Comprehensive Cancer Network highlighted several challenges in the operationalization of biosimilars in a clinical practice setting.<sup>18</sup> These challenges include medication, storage, dispensing errors, excessive financial burden to patients, economic challenges for institutions/providers, and payer policies and preferences, such as the need for a specific (biosimilar or originator) product.<sup>18</sup> A detailed discussion of these challenges and potential solutions is beyond the scope of the current review but is available in recent publications on the implementation of biosimilars in clinical settings.<sup>19–22</sup>

### Economics of Biosimilars

As of September 2022, 71 and 37 biosimilars are approved in the EU and United States, respectively.<sup>23,24</sup> These biosimilars are estimated to have saved the EU \$11.8 billion between 2016 and 2022.<sup>25</sup> In fields with common biosimilar use (e.g., oncology), the cost savings associated with prescribing

**Fig. 1.** Comparison of the drug approval pathways for originator drugs and biosimilars in the United States and EU. PK, pharmacokinetics.



biosimilars could be used for budget-neutral expansion of treatment access for patients. In an economic modeling simulation comparing the average sales price of reference pegfilgrastim to a biosimilar, the cost savings of the biosimilar ranged from \$1.3 million (at a 15% price discount) to \$3 million (a 35% discount); these savings could be used to provide biosimilar pegfilgrastim to an additional 352 to 1,076 patients.<sup>26</sup> The price competition between biosimilars and reference products can also decrease the cost of the reference products; a 4%–17% decrease in the compound annual growth rate of the price of reference biologics was observed in the United States in 2021.<sup>27</sup> Furthermore, reduced medication costs can improve a patient's treatment adherence and thereby result in improved health outcomes<sup>28</sup>; this can reduce the financial burden on the health care system because nonadherence is a key contributor to overall health care costs.<sup>29</sup>

### Approved Biosimilars in Ophthalmology

Razumab (Intas Pharmaceuticals), a ranibizumab biosimilar, was the world's first approved ophthalmic biosimilar. This ranibizumab biosimilar was approved only in India in 2015<sup>30</sup> for all the same indications as ranibizumab: nAMD, DME, RVO, and mCNV. Although results from a large real-world safety study showed no new ocular or systemic safety concerns,<sup>31</sup> reports of ocular inflammation prompted the Vitreo Retina Society of India to issue an advisory against some batches of Razumab,<sup>32</sup> which is not approved outside India.

In the United States and EU, ranibizumab-nuna (Byooviz; Samsung Bioepis and Biogen) was approved in 2021 as the first biosimilar for ranibizumab.<sup>9,10</sup> A global, randomized Phase 3 study confirmed the

similarity in efficacy, safety, and immunogenicity profiles of ranibizumab-nuna and reference ranibizumab in patients with nAMD.<sup>33</sup> The primary endpoint of non-inferiority was met: The least squares mean change in best-corrected visual acuity was 6.2 letters with ranibizumab-nuna versus 7.0 letters with reference ranibizumab (adjusted treatment difference:  $-0.8$  letters [90% CI,  $-1.8$ – $0.2$ ]). The least squares mean change in CST was  $-108$   $\mu\text{m}$  with ranibizumab-nuna versus  $-100$   $\mu\text{m}$  with reference ranibizumab (adjusted treatment difference:  $-8$   $\mu\text{m}$  [95% CI,  $-19$ – $3$ ]). Immunogenicity was low, and adverse events were similar between treatment groups.<sup>33</sup> In the EU, ranibizumab-nuna was approved for all indications of reference ranibizumab.<sup>10</sup> In the United States, however, ranibizumab-nuna was not approved for all reference ranibizumab indications; it was not approved for DR and DME<sup>9</sup> because the evaluated dose of ranibizumab-nuna during the clinical trials was 0.5 mg, whereas the approved dosage of reference ranibizumab for diabetic indications is 0.3 mg.<sup>4</sup>

Recently, ranibizumab-eqrn (Cimerli; Formycon, Bioeq, Coherus Biosciences) was deemed by the FDA as the second approved biosimilar and first interchangeable biosimilar in the United States for ranibizumab.<sup>34</sup> This approval was based on the global, Phase 3 randomized trial of ranibizumab-eqrn, which demonstrated comparable efficacy, safety, and immunogenicity of ranibizumab-eqrn to reference ranibizumab in patients with nAMD.<sup>35</sup> Similar improvements in best-corrected visual acuity were observed in both treatment groups: Patients saw  $\sim 5$  more letters after 8 weeks of treatment with either ranibizumab-eqrn or ranibizumab. As the 90% CI ( $-1.6$ – $0.9$ ) was within the predefined equivalence margin ( $-3.5$ – $3.5$ ), the primary endpoint confirmed the similarity of

ranibizumab-eqrn to ranibizumab. Submissions for biosimilar approval of ranibizumab-eqrn were filed with the European Medicines Agency in 2021.<sup>35</sup> There are currently no approved aflibercept biosimilars, but several are in development and are described in the following section. Similarly, no bevacizumab biosimilars are approved for ophthalmic use; this is not surprising because reference bevacizumab is also not approved to treat retinal diseases. In oncology, however, two bevacizumab biosimilars are approved in the United States and EU: bevacizumab-bvzr (Zirabev; Pfizer) and bevacizumab-awwb (Mvasi; Amgen).<sup>23,24</sup> Four additional bevacizumab biosimilars are approved in the EU only: Abevmy (Biocon/Viatris), Alymsys/Oyavas (mAbxience), Aybintio (Samsung Bioepis), and Onbevzi (Samsung Bioepis).<sup>23</sup>

To address a temporary supply shortage of reference bevacizumab in the United States, some payers suggested the use of approved bevacizumab biosimilars in the interim.<sup>36</sup> This suggestion was protested by the American Academy of Ophthalmology and American Society of Retina Specialists because these biosimilars have not been tested for ophthalmic use, and one of the biosimilar formulations, Zirabev (bevacizumab-bvzr), includes a buffering agent that may be toxic to the retina.<sup>36</sup> Of note, biosimilar formulations are permitted to have minor differences in clinically inactive components compared with the reference product, as long as the biological product has demonstrated similarity to the reference product.<sup>37</sup>

**Anti-VEGF Biosimilars in Development**

*Ranibizumab*

The patents for ranibizumab have expired in the United States and the EU.<sup>38</sup> One ranibizumab biosimilar

is currently in development in the United States and EU (Table 2).

Xlucane (Xbrane Biopharma, Bausch + Lomb, and Stada Arzneimittel): A pivotal, Phase 3, randomized trial demonstrated that Xlucane and reference ranibizumab had equivalent efficacy at the 6-month interim readout in patients with nAMD.<sup>39</sup> No clinically meaningful differences in safety, immunogenicity, and pharmacokinetics were identified between Xlucane and reference ranibizumab, although detailed data are currently unavailable.<sup>39</sup>

*Aflibercept*

The U.S. and EU aflibercept patents will expire between 2023 and 2027.<sup>38</sup> Six aflibercept biosimilars are in clinical development in the United States and EU (Table 2).

MYL-1701P (Mylan and Momenta): A global, Phase 3 trial evaluating the safety and efficacy of MYL-1701P versus reference aflibercept in 324 patients with DME was completed in October 2021.<sup>40</sup>

SB-15 (Samsung Bioepis): A global, Phase 3 clinical trial evaluating the efficacy, safety, pharmacokinetics, and immunogenicity of SB15 compared with aflibercept in nAMD is complete, with results expected in the second half of 2022.<sup>41</sup>

ABP 938 (Amgen): A global, Phase 3 study evaluating the efficacy and safety of ABP 938 compared with aflibercept in nAMD is underway. The first data are expected in 2022, and the study is estimated to end in 2023.<sup>42</sup>

CT-P42 (Celltrion): A Phase 3 study evaluating the efficacy and safety of CT-P42 compared with aflibercept in DME is currently recruiting participants; the study is expected to be completed in 2022.<sup>43</sup>

FYB203 (Formycon/Bioeq): A global, Phase 3 study evaluating the efficacy and safety of FYB203

Table 2. Ranibizumab, Aflibercept, and Bevacizumab Biosimilars in Clinical Development in the EU and United States

Reference Product	Biosimilar	Trial Number	Manufacturer	Stage
Ranibizumab	Xlucane	NCT03805100	Xbrane Biopharma, Bausch + Lomb, and Stada Biopharma	Planned submission to EMA and FDA
Aflibercept	MYL-1701P	NCT03610646	Mylan and Momenta	Phase 3, completed
	SB15	NCT04450329	Samsung Bioepis	Phase 3, active
	ABP 938	NCT04270747	Amgen	Phase 3, active
	CT-P42	NCT04739306	Celltrion	Phase 3, active
	FYB203	NCT04522167	Bioeq	Phase 3, active
	SOK583A1	NCT04864834	Amgen	Phase 3, recruiting
Bevacizumab	ONS-5010	NCT03844074, NCT03834753	Outlook Therapeutics	Submitted to FDA as new BLA

EMA, European Medicines Agency; BLA, Biologics License Application.

compared with aflibercept in nAMD is currently recruiting participants and is expected to be completed in 2022.<sup>44</sup>

SOK583A1 (Sandoz): A global, Phase 3 study evaluating the efficacy, safety, and immunogenicity of SOK583A1 in patients with nAMD is recruiting and is expected to be completed in 2023.<sup>45</sup>

### *Bevacizumab*

The U.S. patents for bevacizumab have expired, and the EU patents are set to expire in 2022.<sup>38</sup> As bevacizumab is a commonly used off-label treatment for nAMD, biosimilar development of this biologic is of interest in the ophthalmic space. Outlook Therapeutics is currently investigating an ophthalmic-labeled bevacizumab biosimilar, ONS-5010, in three clinical trials (NORSE ONE, NORSE TWO, and NORSE THREE) in patients with nAMD.<sup>46</sup> As an ophthalmic bevacizumab biosimilar, ONS-5010 is required to have less particulate matter than the intravenous formulations.<sup>46</sup> Unlike submissions for biosimilar approval, which can be based on only one clinical trial, multiple trials were needed because Outlook Therapeutics has submitted a new Biologics License Application for ONS-5010 to the FDA.<sup>47</sup> The NORSE TWO trial, completed in the United States in 2021, evaluated whether the safety and efficacy of monthly ONS-5010 (1.25 mg) were superior to ranibizumab dosed using the PIER study protocol (fixed quarterly 0.5-mg injections after three-monthly loading doses).<sup>47</sup> The primary endpoint was met, with 41.0% of patients receiving ONS-5010 compared with 24.7% of patients receiving ranibizumab gaining  $\geq 15$  letters of best-corrected visual acuity.<sup>47</sup> The safety profile of ONS-5010 was similar to previous off-label bevacizumab data and to previous studies of ONS-5010.<sup>47</sup>

The approval of ONS-5010 for nAMD may have an interesting impact on the off-label use of bevacizumab, which is compounded to make it suitable for IVI. Once ONS-5010 enters the market, compounding originator bevacizumab for ophthalmic use may no longer be justifiable without patient-specific prescriptions at 503a pharmacies or allowed by the FDA in 503b pharmacies,<sup>48</sup> and the singular market share position of ONS-5010 may result in a higher price for the ophthalmic bevacizumab biosimilar. However, the FDA-required justification for compounded medications is currently only mandatory for generic medications<sup>48</sup> and may not be applicable to biologics, so time will tell whether the requirements change as biosimilars become more commonly used. Moreover, unlike biosimilar extrapolation to all the reference product's indications, ONS-5010 will need to undergo additional

clinical trials to receive any possible label expansion in addition to nAMD.

## Conclusions

As new biosimilars are developed and the major anti-VEGF drug patents expire, biosimilars aim to gain a large part of the market share in ophthalmology. Because of the high costs of biologics and the rapidly increasing costs of health care overall, potential financial savings from biosimilar use can have a significant impact on patients, physicians, payers, and health care systems. Increased education and awareness for ophthalmologists can enhance support for the adoption of new biosimilars, with the potential to reduce economic burden, increase treatment adherence, and ultimately improve outcomes in ophthalmology.

**Key words:** age-related macular degeneration, aflibercept, biosimilar, biologic, bevacizumab, choroidal neovascularization, diabetic macular edema, neovascular AMD, ranibizumab, retinal edema.

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## References

1. Kaiser SM, Arepalli S, Ehlers JP. Current and future anti-VEGF agents for neovascular age-related macular degeneration. *J Exper Pharmacol* 2021;13:905–912.
2. VABYSMO™ (faricimab-svoa) injection, for intravitreal use. Prescribing information. San Francisco, CA: Genentech, Inc; 2022.
3. BEOVU® (brolicizumab-dblb) injection, for intravitreal use. Prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.
4. LUCENTIS® (ranibizumab injection) for intravitreal injection. Prescribing information. San Francisco, CA: Genentech, Inc.; 2018.
5. EYLEA® (aflibercept) injection, for intravitreal use. Prescribing information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2021.
6. Bauman CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolicizumab. *Ophthalmology* 2020;127:1345–1359.
7. Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 Medicare fee-for-service part B claims file. *Am J Ophthalmol* 2011;151:887–895.e1.
8. Polat O, İnan S, Özcan S, et al. Factors affecting compliance to intravitreal anti-vascular endothelial growth factor therapy in

- patients with age-related macular degeneration. *Turk J Ophthalmol*. 2017;47:205–210.
9. Drug development delivery. FDA approves samsung bioepis & biogen's BYOOVIZ (SB11), LUCENTIS biosimilar (ranibizumab-nuna). News report. Drug development & delivery website. Available at: <https://drug-dev.com/fda-approves-samsung-bioepis-biogens-byooviz-sb11-lucentis-biosimilar-ranibizumab-nuna/>. Accessed November 3, 2022.
  10. European commission. Union register of medicinal products for human use. Available at: <https://ec.europa.eu/health/documents/community-register/html/h1572.htm>. Accessed November 3, 2022.
  11. US food and drug administration. Biosimilar and interchangeable products. Available at: <https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products>. Accessed September 6, 2019.
  12. US department of health and human services. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. 2015. Available at: <https://www.fda.gov/media/82647/download>. Accessed November 3, 2022.
  13. European medicines agency. Biosimilars in the EU. Information guide for healthcare professionals. Available at: [https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals\\_en.pdf](https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf). Accessed November 3, 2022.
  14. European medicines agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues. Available at: [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active\\_en-2.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf). Accessed November 3, 2022.
  15. US department of health and human services. Nonproprietary naming of biological products guidance for industry. Available at: <https://www.fda.gov/media/93218/download>. Accessed November 3, 2022.
  16. Schiestl M, Stangler T, Torella C, et al. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nat Biotechnol* 2011;29:310–312.
  17. Declerck P, Farouk-Rezk M, Rudd PM. Biosimilarity versus manufacturing change: two distinct concepts. *Pharm Res* 2016; 33:261–268.
  18. Handel E, Koh WJ, Ray L. NCCN Pharmacy Directors Forum Recommendations on Operationalizing the Safe and Efficient Use of Biosimilars in the Clinical Setting. Available at: [https://www.nccn.org/docs/default-source/default-document-library/2021\\_nccn\\_white\\_paper\\_safe\\_and\\_efficient\\_use\\_of\\_biosimilars.pdf?sfvrsn=b97c32c7\\_2](https://www.nccn.org/docs/default-source/default-document-library/2021_nccn_white_paper_safe_and_efficient_use_of_biosimilars.pdf?sfvrsn=b97c32c7_2). Accessed November 3, 2022.
  19. Lam SW, Amoline K, Marcum C, Leonard M. Healthcare system conversion to a biosimilar: trials and tribulations. *Am J Health Syst Pharm* 2021;78:2159–2163.
  20. Kar I, Kronz M, Kolychev E, et al. Biosimilar strategic implementation at a large health system. *Am J Health Syst Pharm* 2022;79:268–275.
  21. Bhardwaja B, Klocke S, Ekinci E, et al. Switching from biologic to biosimilar products: insight from an integrated health care system. *BioDrugs* 2022;36:1–11.
  22. Humphreys SZ. Real-world evidence of a successful biosimilar adoption program. *Future Oncol* 2022;18:1997–2006.
  23. European medicines agency. Medicines. Available at: [https://www.ema.europa.eu/en/medicines/search\\_api\\_aggregation\\_ema\\_medicine\\_types/field\\_ema\\_med\\_biosimilar](https://www.ema.europa.eu/en/medicines/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar). Accessed November 3, 2022.
  24. US food and drug administration. Biosimilar product information. Available at: <https://www.fda.gov/drugs/biosimilars/biosimilar-product-information>. Accessed November 3, 2022.
  25. IQVIA institute for human data science. Advancing biosimilar sustainability in europe. 2018. Available at: [https://www.biosimilars-nederland.nl/wp-content/uploads/2018/10/okt\\_2018\\_IQVIA\\_Pfizer\\_Advancing-Biosimilar-Sustainability-in-Europe.pdf](https://www.biosimilars-nederland.nl/wp-content/uploads/2018/10/okt_2018_IQVIA_Pfizer_Advancing-Biosimilar-Sustainability-in-Europe.pdf). Accessed November 3, 2022.
  26. McBride A, Wang W, Campbell K, et al. Economic modeling for the US of the cost-efficiency and associated expanded treatment access of conversion to biosimilar pegfilgrastim-bmez from reference pegfilgrastim. *J Med Econ* 2020;23, 856–863.
  27. Amgen Inc. Amgen 2021 biosimilar trend report. Available from: [https://www.amgenbiosimilars.com/commitment/-/media/Themes/Amgen/amgenbiosimilars-com/Amgenbiosimilars-com/pdf/USA-CBU-80962\\_Amgen-2021-Biosimilar-Trends-Report.pdf](https://www.amgenbiosimilars.com/commitment/-/media/Themes/Amgen/amgenbiosimilars-com/Amgenbiosimilars-com/pdf/USA-CBU-80962_Amgen-2021-Biosimilar-Trends-Report.pdf). Accessed November 3, 2022.
  28. Jackson S, Stokes JP. Impact of out-of-pocket costs on patient initiation, adherence and persistence rates for patients treated with anti-vascular endothelial growth factor medicines. *Clin exp ophthalmol* 2020;48:477–485.
  29. Iuga AO, McGuire MJ. Adherence and health care costs. *Risk Manag Healthc Policy* 2014;7:35–44.
  30. Intas launches RAZUMAB, Globally the first biosimilar to lucentis® (Ranibizumab). News release. PRNewswire; June 19, 2015. Available at: <https://www.prnewswire.com/in/news-releases/intas-launches-razumab-globally-the-first-biosimilar-to-lucentis-ranibizumab-508383021.html>. Accessed November 3, 2022.
  31. Chakraborty D, Stewart MW, Sheth JU, et al. Real-world safety outcomes of intravitreal ranibizumab biosimilar (razumab) therapy for chorioretinal diseases. *Ophthalmol ther* 2021; 10:337–348.
  32. Mukherjee R Advisory Issued Against Retinal Disease Drug. Mumbai, India: Times of India. 2019. Available at: <https://timesofindia.indiatimes.com/business/india-business/advisory-issued-against-retinal-disease-drug/articleshow/68005152.cms>. Accessed November 3, 2022.
  33. Woo SJ, Veith M, Hamouz 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* 2021;139:68–76.
  34. CIMERLI™ (Ranibizumab-eqm) Injection, for intravitreal use. Prescribing information. Redwood City, CA: Coherus BioSciences, Inc; 2022.
  35. FYB201 Ranibizumab biosimilar candidate. Pipeline. Martinsried/Planegg, Germany: Formycon AG. Available at: <https://www.formycon.com/en/biosimilars/fyb201/>. Accessed November 3, 2022.
  36. Insurance companies are pushing biosimilar drugs that may damage vision. News release. American academy of ophthalmology. July 29, 2021. Available at: <https://www.aaopt.org/newsroom/news-releases/detail/insurance-companies-are-pushing-biosimilar-drugs>. Accessed November 3, 2022.
  37. US department of health and services. Questions and answers on biosimilar development and the BPCI act. Guidance for Industry. Available at: <https://www.fda.gov/media/119258/download>. Accessed November 3, 2022.
  38. GaBI Journal Editor. Patent expiry dates for biologicals: 2018 update. *GaBI J* 2018;8:24–31.
  39. Xlucane™ meets the primary endpoint in the Pivotal phase III trial with xlucane™ – Regulatory submission in EU and US planned for second half of 2021. News release. Stockholm,

- Sweden: Xbrane Biopharm AB. Available at: [https://xbrane.com/en/mfn\\_news\\_en/xlucane-meets-the-primary-endpoint-in-the-pivotal-phase-iii-trial-with-xlucane-regulatory-submission-in-eu-and-us-planned-for-second-half-of-2021/](https://xbrane.com/en/mfn_news_en/xlucane-meets-the-primary-endpoint-in-the-pivotal-phase-iii-trial-with-xlucane-regulatory-submission-in-eu-and-us-planned-for-second-half-of-2021/). Accessed November 3, 2022.
40. Comparative study to evaluate the efficacy and Safety of MYL-1701P and Eylea® in Subjects with diabetic macular edema. Good clinical practice network website. Available at: <https://ichgcp.net/clinical-trials-registry/NCT03610646>. Accessed November 3, 2022.
  41. A study to compare SB15 (Proposed aflibercept biosimilar) to eylea in subjects with neovascular age-related macular degeneration (AMD). Clinicaltrials.gov Identifier: NCT04450329. Available at: <https://clinicaltrials.gov/ct2/show/NCT04450329>. Accessed November 3, 2022.
  42. A study to understand effectiveness and safety of ABP 938 compared to aflibercept (Eylea®) in Patients suffering with neovascular age-related macular degeneration [neovascular (Wet) AMD]. ClinicalTrials.gov Identifier: NCT04270747. Available at: <https://clinicaltrials.gov/ct2/show/NCT04270747>. Accessed November 3, 2022.
  43. Study to compare efficacy and safety of CT-P42 in Comparison with eylea in patients with diabetic macular edema. ClinicalTrials.gov Identifier: NCT04739306. Available at: <https://clinicaltrials.gov/ct2/show/NCT04739306>. Accessed November 3, 2022.
  44. Efficacy and safety of the aflibercept FYB203 biosimilar in comparison to eylea® in patients with neovascular Age-related macular degeneration (MAGELLAN-AMD). Clinicaltrials.gov identifier: NCT04522167. Available at: <https://clinicaltrials.gov/ct2/show/NCT04522167>. Accessed November 3, 2022.
  45. US national library of medicine. Phase III study Assessing the efficacy, Safety and immunogenicity of SOK583A1 versus eylea® in patients with neovascular age-related macular degeneration (Mylight). Clinicaltrials.gov identifier: NCT04864834. Available at: <https://clinicaltrials.gov/ct2/show/NCT04864834>. Accessed November 3, 2022.
  46. Outlook therapeutics presents NORSE TWO phase 3 pivotal safety and efficacy data for ONS-5010/LYTENAVA™ (bevacizumab-vikg) at the Retina subspecialty day, 2021. Available at: <https://www.globenewswire.com/news-release/2021/11/13/2333715/0/en/Outlook-Therapeutics-Presents-NORSE-TWO-Phase-3-Pivotal-Safety-and-Efficacy-Data-for-ONS-5010-LYTENAVA-bevacizumab-vikg-at-the-Retina-Subspecialty-Day-American-Academy-of-Ophthalmology.html>. Accessed November 3, 2022.
  47. Kunzmann K. Bevacizumab formulation significantly improves wAMD vision versus ranibizumab in NORSE 2. HCP live website. November 13, 2021. Available at: <https://www.hcplive.com/view/bevacizumab-formulation-wamd-vision-versus-ranibizumab-norse-2>. Accessed November 3, 2022.
  48. US department of health and human services. Hospital and health system compounding under section 503A of the federal Food, Drug, and Cosmetic Act. Guidance for industry. 2021. Available at: <https://www.fda.gov/media/97353/download>. Accessed November 3, 2022.