Competition law and pricing among biologic drugs: the case of VEGF therapy for retinal diseases

Victor L. Van de Wiele¹, Maximilian Hammer², Ravi Parikh³,⁴, William B. Feldman¹, Ameet Sarpalwari¹ and Aaron S. Kesselheim¹,*

¹Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
²Institute of Physiology and Pathophysiology, Heidelberg University, Heidelberg, Germany
³Department of Ophthalmology and Visual Sciences, New York University School of Medicine, New York, NY, USA
⁴Manhattan Retina and Eye Consultants, New York, NY, USA
*Corresponding author. E-mail: akesselheim@bwh.harvard.edu

ABSTRACT

Neovascular age-related macular degeneration (AMD) is a progressive eye disease and is a leading cause of vision loss in the Western world. Vascular endothelial growth factor inhibitors have become a mainstay of treatment for this disease. Currently, treatment options include three originator biologics with approvals for neovascular AMD (aflibercept, ranibizumab, and brolucizumab-dbll) and one biologic that is commonly used off-label for the condition (bevacizumab). In the USA, Medicare spending on these drugs consistently surpassed $4 billion per year between 2015 and 2019, driven by high prices and varying off-label use of bevacizumab, which is substantially cheaper than the other biologics used to treat neovascular AMD. In this article, we discuss how legal reform can improve market competition for biologic drugs, using AMD therapies as a case study. We chose this group of drugs for their significant contribution to Medicare spending, the price difference between approved therapies and intravitreal bevacizumab, and because there currently exists a large biosimilar pipeline with many drug candidates in the final stage of development. We propose mechanisms for anticipating and facilitating the market introduction of biosimilars, as well as changes to the pricing model in Medicare that can promote use of cost-effective therapies. Reforms such as empowering Medicare to negotiate drug
prices may help ensure that introduction of new biologics and biosimilars for AMD will lower spending and increase patient access.

**KEYWORDS:** competition law, drugs, pricing, anti-VEGF, ophthalmology, Medicare

Neovascular age-related macular degeneration (AMD) is a progressive eye disease characterized by growth and exudation from new blood vessels under the retina and is a leading cause of vision loss in the Western world.¹ In the USA, as many as 11 million people have some form of neovascular AMD—a number expected to double by 2050.² Vascular endothelial growth factor (VEGF) inhibitors have become a mainstay of treatment for this disease. These agents, originally developed to treat cancer, improve visual acuity in neovascular AMD when given by intravitreal injection (into the eye) and are now used to treat a number of retinal diseases, including diabetic retinopathy and macular edema following retinal vein occlusions.³,⁴ The first anti-VEGF monoclonal antibody to receive US Food and Drug Administration (FDA) approval was bevacizumab (Avastin) in 2004; though it was approved for colorectal cancer, it has been used off-label for many years to treat neovascular AMD.⁵ Ranibizumab (Lucentis), another monoclonal antibody, and aflibercept (Eylea), a recombinant fusion protein or trap molecule,⁶ were approved by the FDA in 2006 and 2011, respectively, to treat neovascular AMD. Clinical trials have demonstrated similar efficacy and safety of all three agents in neovascular AMD.⁷,⁸

Despite important clinical benefits, anti-VEGF drugs are costly. The global anti-VEGF market for retinal diseases exceeded $7.0 billion in 2020,⁹ and VEGF inhibitors are among the highest-cost drugs for Medicare, with $5.21 billion in fee-for-service

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¹ Fact Sheet, BrightFocus Foundation, Age-related Macular Degeneration: Facts & Figures (Jan. 5, 2019), https://www.brightfocus.org/macular/article/age-related-macular-facts-figures; Nvision, A Timeline to Macular Degeneration: How Long Until Sight Loss? (Dec. 22, 2018), https://www.nvisioncenters.com/macular-degeneration/sight-loss-timeline/.
² Id.
³ Ribatti D, Folkman J, A Pioneer in the Study of Angiogenesis, 11 Angiogenesis 1, 3–10 (2008).
⁴ Miller JW et al., Vascular Endothelial Growth Factor/Vascular Permeability Factor Is Temporally and Spatially Correlated with Ocular Angiogenesis in a Primate Model, 145 Am. J. Pathol. Sep. 3, 574–84 (1994).
⁵ FDA, Avastin FDA Approval Letter (Feb. 26, 2004), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/STN-125085_Avastin_Approv.pdf
⁶ FDA, Lucentis FDA Approval Letter (June 30, 2006), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s000_Lucentis_APPROV.pdf; FDA, Eylea FDA Approval Letter (Nov. 18, 2011), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000Approv.pdf
⁷ CATT Research Group, Ranibizumab and Bevacizumab for Neo-Vascular Age-Related Macular Degeneration, 364 N. Engl. J. Med. 1897–908 (2011); Chakravarthy U et al., IVAN Study Investigators, Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation: 2-Year Findings of the IVAN Randomised Controlled Trial, 382 Lancet 9900, 1258–67 (2013); Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group et al, Ranibizumab and Bevacizumab for Treatment of Neovascular Age-Related Macular Degeneration: Two-Year Results, 119 Ophthalmology 7, 1388–98 (2012).
⁸ Dakin HA et al., Cost-Effectiveness of Ranibizumab and Bevacizumab for Age-Related Macular Degeneration: 2-Year Findings from the IVAN Randomized Trial, 4 BMJ Open, e005094 (2014).
⁹ ReportLinker, Macular Degeneration Treatment Market—Growth, Trends, Covid-19 Impact, and Forecasts (2021–2026) (May 2021), https://www.reportlinker.com/p06074771/Macular-Degeneration-Treatment-Market-Growth-Trends-COVID-19-Impact-and-Forecasts.html?utm_source=GNW.
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spending (including for cancer-related uses) reported in 2019. However, while aflibercept and ranibizumab were available in 2019 at an average sales price (ASP) of $1877 and $1717 per dose, off-label use of bevacizumab for retinal diseases is far less expensive (about $70/dose). Given these price differences, off-label bevacizumab has become the standard of care at many US medical centers and in several European countries. Bevacizumab was the most commonly used anti-VEGF to treat retinal disease in the USA from 2006 until 2015 among Medicare Advantage and privately insured patients. Such use of bevacizumab has been controversial, since it requires sterile compounding, a technique that can be risky if not done properly. Partially for this reason, bevacizumab injections for retinal diseases in the UK constituted only 3 per cent of total injections in 2015. However, increased rates of vision threatening eye infections have not been seen with compounded bevacizumab compared with other medications in large-scale studies.

The first new anti-VEGF treatment for retinal diseases in nearly a decade, brolucizumab-dbll (Beovu), was approved by the FDA in October 2019. This drug was expected to lower the spending on treating neovascular AMD, given that aflibercept and ranibizumab prices had stagnated at high levels between 2013 and 2017. But brolucizumab-dbll was launched at a comparable list price of $1850 per dose. Numerous additional anti-VEGF biosimilar products are now poised to enter the US market due to the expiration of key patents on aflibercept, ranibizumab, and bevacizumab.

In this paper, we review trends in the prices for these drugs over the past 15 years and seek to identify market, regulatory, legal, and clinical factors that have affected competition. We use anti-VEGF drugs as a case example because they account for high Medicare spending, the wide gap in prices between an off-label drug and its on-label counterparts, and because there are a lot of biosimilars in the pipeline. Anti-VEGF drugs can serve as

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10 CMS.gov, Medicare Part B Portal: Bevacizumab, Aflibercept, Ranibizumab (accessed Feb. 9, 2021), https://portal.cms.gov/wps/portal/unauthportal/unauthmicrostrategyreportslink?evtex=2048001&src=mstrWeb.2048001&objectID=AEC7511A11E817EF2FBA0080EFC5E3D8&visMode=0&currentrViewMedia=1&Server=E48V126P&Project=OIPDA.
11 Id.
12 Glasser DB et al., Intravitreal Anti-Vascular Endothelial Growth Factor Cost Savings Achievable with Increased Bevacizumab Reimbursement and Utilization, Ophthalmology 127(12), 1688–1692 (2020).
13 https://www.aao.org/eye-health/diseases/avastin-eylea-lucentis-difference (Feb. 2020).
14 Parikh R et al., Trends of Anti-Vascular Endothelial Growth Factor Use in Ophthalmology Among Privately Insured and Medicare Advantage Patients, 124 Ophthalmology 3, 352–8 (2017).
15 Shalaby AK et al., Licence to Save: A UK Survey of Anti-VEGF Use for the Eye in 2015, 30 Eye (Lond) 11, 1404–6 (2016).
16 VanderBeek BL, Bonaffini SG, Ma L, Association of Compounded Bevacizumab with Postinjection Endophthalmitis, 133 JAMA Ophthalmol. 10, 1159–64 (2015).
17 FDA, Beovu FDA Approval Letter (Oct. 7, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761125Orig1s000Approv.pdf.
18 Parikh R et al., Comparison of Ophthalmic Medication Prices between the United States and Australia [published correction appears in JAMA Ophthalmol. May 9, 2019], 137 JAMA Ophthalmol, 4, 358–62 (2019).
19 Jacob Bell, Eylea Casts a Shadow over Novartis’ Latest Approval (Oct. 8, 2019), https://www.biopharma.dive.com/news/novartis-beovu-approval-wet-amd-regeneron-eylea/564578/.
20 Sharma A et al., Biosimilars in Ophthalmology: ‘Is There a Big Change on the Horizon?’, 24 Clin. Ophthalmol. 12, 2137–43 (2018).
a good case example for other biologic drugs facing similar market conditions. Many monoclonal antibodies, for example, already experience or will experience biosimilar competition in the near future as their key patents expire. The off-label alternative of bevacizumab in turn demonstrates how lower priced medications, either biosimilars or cheaper originator biologics, can trigger much needed savings for both Medicare and patients.

I. DEVELOPMENT OF ANTI-VEGF ANTIBODY TREATMENT FOR NEOVASCULAR AMD

When bevacizumab received its first FDA approval for colorectal cancer in 2004, clinical trials were already underway for neovascular AMD-specific uses of anti-VEGF therapy (See Figure 3). Clinicians started using bevacizumab for neovascular AMD in 2005, following experience published by Philip Rosenfeld at the Bascom Palmer Eye Institute in Miami.21,22,23 Adapting bevacizumab for such use required sterile compounding of the drug from its intravenous form into syringes that could be injected intravitreally to avoid complications such as microbial contamination. Rosenfeld found that these injections were clinically effective in treating neovascular AMD, and subsequent studies confirmed that bevacizumab was well-tolerated and associated with a rapid regression of retinal and iris neovascularization, thereby reducing vision loss.24

Despite evidence of bevacizumab’s effectiveness and safety for neovascular AMD, its manufacturer, Genentech, did not seek to expand its labeling to cover this use. Genentech had another anti-VEGF monoclonal antibody in the pipeline, ranibizumab, which was approved in June 2006. Ranibizumab was a fragment of the complete anti-VEGF antibody but had the same active site. The smaller protein size also theoretically allows ranibizumab to enter the subretinal space after intravitreal injection, while bevacizumab does not penetrate the retina as well as ranibizumab.25 However, following ranibizumab’s approval, numerous studies in the USA and Europe confirmed no clinically relevant differences when comparing bevacizumab to ranibizumab on visual acuity gains for macular degeneration or diabetic macular edema.26,27,28 In 2011,

21 Rosenfeld PJ, Intravitreal Avastin: The Low Cost Alternative To Lucentis?, 142 Am. J. Ophthalmol. 1, 141–3 (2006).
22 Rosenfeld PJ, Fung AE, Puliafito CA, Optical Coherence Tomography Findings after an Intravitreal Injection of Bevacizumab (Avastin) for Macular Edema from Central Retinal Vein Occlusion, 36 Ophthalmic Surg. Lasers Imaging, 4, 336–9 (2005).
23 Rosenfeld PJ, Moshfeghi AA, Puliafito CA, Optical Coherence Tomography Findings after an Intravitreal Injection of Bevacizumab (Avastin) for Neovascular Age-Related Macular Degeneration, 36 Ophthalmic Surg. Lasers Imaging, 4, 331–5 (2005).
24 Avery RL et al., Intravitreal Bevacizumab (Avastin) in the Treatment of Proliferative Diabetic Retinopathy, 113 Ophthalmology, 10, 1695.e1–15 (2006).
25 Terasaki H et al., Penetration of Bevacizumab and Ranibizumab through Retinal Pigment Epithelial Layer In Vitro, 35 Retina, 5, 1007–15 (2015).
26 Id. supra note 7, CATT Research Group.
27 Chakravarthy U et al., A Randomized Controlled Trial to Assess the Clinical Effectiveness and Cost-Effectiveness of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation (IVAN), 19 Health Technology Assessment, 78 (2015); IVAN Study Investigators et al., Ranibizumab versus Bevacizumab to Treat Neovascular Age-Related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial, 119 Ophthalmology, 7, 1399–411 (2012), Erratum in: 119 Ophthalmology, 8, 1508 (2012), Erratum in: 120 Ophthalmology, 9, 1719 (2013).
28 Id. supra note 8, Dakin et al.
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Table 1. Sales of ranibizumab and aflibercept in the USA, 2010–19

| Year | Ranibizumab sales (USD million) | Aflibercept sales (USD million) |
|------|---------------------------------|---------------------------------|
| 2010 | 1,458                           | —                               |
| 2011 | 1,523                           | —                               |
| 2012 | 1,481                           | 838                             |
| 2013 | 1,689                           | 1,400                           |
| 2014 | 1,701                           | 1,736                           |
| 2015 | 1,520                           | 2,676                           |
| 2016 | 1,406                           | 3,320                           |
| 2017 | 1,414                           | 3,700                           |
| 2018 | 1,659                           | 4,080                           |
| 2019 | 1,826                           | 4,644                           |

Note: Numbers directly reported by the manufacturers.

the FDA approved aflibercept as a third anti-VEGF medication to treat neovascular AMD, and subsequently for diabetic macular edema and macular edema for retinal vein occlusions.

These three products remained for many years as the only anti-VEGF medications available for patients with neovascular AMD. Annual sales of ranibizumab since launch have averaged $1.568 billion in the USA. Aflibercept, which is the only therapy approved for administration every 8 weeks and also has a 12-week dosing schedule possibility (the others are approved for monthly administration), doubled its sales revenue in its second year on the market and kept rising through 2019 when US sales reached $4.6 billion (Table 1).

Medicare has been the primary payor for anti-VEGF neovascular AMD therapy in the USA since the disease affects older adults. Within Medicare, these products are generally covered by Part B because they are physician-administered. Medicare Part B requires patients to pay monthly premiums and annual deductibles. Once a deductible is met, the patient typically pays 20 per cent co-insurance for prescription drugs. Medicare Part B reimbursement is equal to the drug’s ASP (net of rebates and other discounts) in the commercial market plus a percentage to cover administration fees (previously 6 per cent but now 4.3 per cent due to sequestration required by the Budget Control Act of 2011).

Figure 1 shows annual spending in recent years on neovascular AMD drugs through fee-for-service Medicare Part B (which includes approximately 65 per cent of all

29 Roche, Historic Quarterly Reporting (last visited on Aug. 4, 2021), https://www.roche.com/investors/historic-quarterly-reporting.htm.
30 Annual Report, Regeneron, More Science, More Impact (2019), https://investor.regeneron.com/static-files/cbebda5b-c02d-466b-8be9-e0d8a4052cf8
31 Id. supra note 29, Roche.
32 Id. supra note 30, Regeneron.
33 CMS.gov, Part B costs (last visited on Aug. 4, 2021), https://www.medicare.gov/your-medicare-costs/part-b-costs
34 Schrag D, Reimburising Wisely? CMS’s Trial of Medicare Part B drug Payment Reform, 374 N. Engl. J. Med. 374, 2101–5 (2016).
35 Budget Control Act 2011.
Medicare Part B spending on drug treatment for wet AMD. Medicare Part B covers bevacizumab for neovascular AMD, but the database does not provide information how much of the spending number pertains to cancer or ophthalmologic use.

Medicare beneficiaries, with the remaining 35 per cent in Medicare Advantage plans). Overall spending on the 3 agents increased 37 per cent from $3.8 billion in 2013 to $5.2 billion in 2019. This was due to increased use—with the total number of claims rising by 52 per cent from 2.0 million to 3.0 million and the number of beneficiaries filling those claims rising 41 per cent from 0.4 million to 0.6 million—while prices largely remained flat. Nearly all of the growth in use and resulting spending can be attributed to aflibercept; spending increased 145.8 per cent from $1.18 billion in 2013 to $2.9 billion in 2019 with the number of claims increasing 147 per cent and the number of beneficiaries filling those claims increasing 168 per cent (See Figure 2). One reason for more patients migrating to aflibercept may be its more convenient dosing, although in practice, patients treated with ranibizumab may be extended out past 4 weeks for maintenance doses by their ophthalmologists once they are stable.

II. NEW COMPETITION IN THE MARKET FOR ANTI-VEGF TREATMENTS FOR NEOVASCULAR AMD

The market for anti-VEGF treatments for neovascular AMD will likely see increased competition in the coming years (Appendix). The first new competitor to enter the market was brolucizumab-dbll (Beovu, Novartis), which showed comparable efficacy to aflibercept, but has a more convenient dosing schedule of every 12 weeks.

36 Medicare FAQ, Does Medicare Cover Macular Degeneration (last updated on Mar. 17, 2021), https://www.medicarefaq.com/faqs/does-medicare-cover-macular-degeneration/.
37 Khurana RN et al., Extended (Every 12 Weeks or Longer) Dosing Interval with Intravitreal Aflibercept and Ranibizumab in Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of VIEW Trials, 200 Am. J. Ophthalmol. 200, 161–8 (2019).
38 Dugel PU et al., HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration, 127 Ophthalmology, 1, 72–84 (2020).
39 Dans KC et al., Durability of Every-8-Week Aflibercept Maintenance Therapy in Treatment-Experienced Neovascular Age-Related Macular Degeneration, 257 Graefes Arch. Clin. Exp. Ophthalmol. 4, 741–8 (2019).
Currently, however, brolucizumab-dbll has limited use due to concerns of intraocular inflammation. The FDA approved the product to treat neovascular AMD in 2019. The American Society of Retinal Specialists also notified its members about 14 reported cases of vasculitis following brolucizumab-dbll injections. Novartis launched an investigation into these post-approval events, which were not observed with other treatments, and updated its labeling to describe this rare potential side effect.

Further competition in the market for anti-VEGF treatments for neovascular AMD will come from biosimilar drugs, which are comparable versions of originator biologics that can be manufactured by different processes and different companies. Congress passed the Biologics Price Competition and Innovation Act (BPCIA) in 2010 to create a pathway for the FDA to approve biosimilars if they were shown to be sufficiently similar to the originator product and if clinical studies demonstrated ‘safety, purity, and potency’ for a use for which the approved product was licensed.

Biosimilars for ranibizumab and aflibercept are under development (see Appendix) and have the potential to create spending changes, although the magnitude of those changes in the US market remains unclear. Two biosimilars, SB11 and FYB201,
were recently found to have highly similar safety and efficacy to ranibizumab.\textsuperscript{43} The FDA accepted an abbreviated Biologics License Application (aBLA) for SB11 on November 18, 2020, while FYB201 manufacturer Formycon submitted an aBLA in the first half of 2021.\textsuperscript{44} The only marketed biosimilars in the USA used to treat neovascular AMD thus far have been bevacizumab biosimilars, although the financial incentives for manufacturers to develop such biosimilars are limited compared with biosimilars for other anti-VEGF treatments given that off-label use of bevacizumab in ophthalmology is so inexpensive. Clinicians may also prefer to see clinical trial evidence of bevacizumab biosimilars being safe and effective for treatment of neovascular AMD. The first biosimilar version of bevacizumab received FDA approval in September 2017 (bevacizumab-awwb [Mvasi], manufactured by Amgen) for several (non-ophthalmologic) indications, including metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, and cervical cancer.\textsuperscript{45} However, due to litigation between Genentech and Amgen over patents on bevacizumab, launch of the product was delayed until July 2019.\textsuperscript{46} In June 2019, a second bevacizumab biosimilar was approved by the FDA (bevacizumab-awwb [Zirabev], manufactured by Pfizer).\textsuperscript{47} It was also delayed by patent litigation but launched in January 2020.

111. GETTING TO A COMPETITIVE MARKET FOR ANTI-VEGF TREATMENTS FOR NEOVASCULAR AMD

Experience with anti-VEGF therapies for neovascular AMD, both in the first period of limited competition, and in the recent more competitive biosimilar market, has revealed important challenges in creating affordable markets for biologic therapeutics.\textsuperscript{48}

A. Bevacizumab: Cost-Effective But Off-Label

Bevacizumab has proven to be an effective, lower cost anti-VEGF therapy for neovascular AMD in numerous studies, even though it is not FDA-approved for this

\textsuperscript{43} Woo SJ 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, 139 JAMA Ophthalmol. 1, 68–76 (2021); Holz FG et al., Efficacy and Safety of Biosimilar FYB201 Compared with Ranibizumab in Neovascular Age-Related Macular Degeneration, 3 Ophthalmology, S0161–6420 (May 2021).

\textsuperscript{44} GlobeNewsWire, Samsung Bioepis and Biogen Announce FDA Filing Acceptance of SB11, A Proposed Biosimilar Referencing Lucentis’ (ranibizumab) (2020), https://www.globenewswire.com/news-release/2020/11/18/2129054/0/en/Samsung-Bioepis-and-Biogen-Announce-FDA-Filing-Acceptance-of-SB11-A-Proposed-Biosimilar-Referencing-Lucentis-ranibizumab.html; Biosimilar Development, Formycon Confirms BLA-Submission Strategy And Timeline For Its Lucentis Biosimilar-Candidate Fyb201 following Consultation with the FDA (2021), https://www.biosimilardevelopment.com/doc/formycon-confirms-bla-submission-strategy-biosimilar-candidate-fyb-following-consultation-fda-0001.

\textsuperscript{45} FDA, FDA Approval Letter Mvasi (Sept. 14, 2017), https://www.accessdata.fda.gov/ucm/groups/fdaclas/documents/document/00761028.pdf.

\textsuperscript{46} Genentech Inc. and City of Hope v Pfizer Inc., C.A. No. 19-638-CFC.

\textsuperscript{47} FDA, FDA Approval Letter Zirabev (June 27, 2019), https://www.accessdata.fda.gov/ucm/groups/fdaclas/documents/document/00761099.pdf.

\textsuperscript{48} Fact Sheet, FTC, FTC Fact Sheet: How Competition Works (last visited Aug. 4, 2021), https://www.consumer.ftc.gov/sites/default/files/games/off-site/youarehere/pages/pdf/FTC-Competition_How-Comp-Works.pdf.
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Health care providers in the USA are free to prescribe drugs off-label if they deem the drug to be medically appropriate for their patients. Marginally lower prices might be expected with the bevacizumab biosimilars. Still, data from the IRIS Registry (Intelligent Research Insight) of the American Academy of Ophthalmology (AAO) show that out of 6,259,470 injections for neovascular AMD from 2013 to 2016, bevacizumab accounted for only 46 per cent, while aflibercept counted for 32 per cent and ranibizumab for 20 per cent. The study also found that bevacizumab injection rates were also declining. Off-label prescribing of bevacizumab is more common in some European Union (EU) countries, where there is often stricter oversight of pharmaceutical reimbursement. For example, in Bulgaria, Romania, Finland, the Netherlands, Ireland, and Portugal, bevacizumab represents 75 per cent or more of the market share for anti-VEGF drugs prescribed to treat neovascular AMD. In contrast, in EU countries such as Denmark, Germany, Spain, and the UK, off-label bevacizumab represents only 3–35 per cent of the market.

The use of bevacizumab to treat neovascular AMD in the USA remains dependent on local factors. For Medicare, the Part B Drug Spending Dashboard does not list Medicare coverage of intravitreal bevacizumab because bevacizumab reimbursement varies from one Medicare administrative contractor (MAC) to another. Each MAC sets an allowable amount based on non-published criteria. For example, Wisconsin Physician Services set its allowable at $90. Medicare payment is 80 per cent of the MAC allowable, minus 2 per cent for sequestration, resulting in a Medicare payment of $70.56 in 2018. MACs are unable to use ASP directly because bevacizumab is a repackaged drug. Some may take supplier pricing into account when setting rates, but no uniform formula exists for calculating payment above costs. This results in a high degree of variation in MAC allowable benchmarks among states.

Private insurance coverage of bevacizumab for neovascular AMD is also variable. For example, United Healthcare Group (UHG) appears to provide coverage of bevacizumab vials for ophthalmic use by providing documentation requirements when prescribed for this indication and acknowledging the compelling evidence of its use for ophthalmologic conditions. Under its coding guidance, UHG states that physicians should check the local coverage determination of the jurisdiction in which they operate.

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49 FDA, Understanding Unapproved Use of Approved Drugs ‘Off-Label’ (last visited Aug. 4, 2021), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label.
50 21 U.S.C. §396.
51 Id. supra note 12, Glasser et al.
52 Report, European Union, Study on Off-Label Use of Medicinal Products in the European Union (2017), https://ec.europa.eu/health/sites/default/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf (p.15).
53 Bro T et al., Off-Label Use of Bevacizumab for Wet Age-Related Macular Degeneration in Europe, 258 Graefes. Arch. Clin. Exp. Ophthalmol. 503–11 (2020).
54 Id.
55 Glasser D et al., Intravitreal Anti–Vascular Endothelial Growth Factor Cost Savings Achievable with Increased Bevacizumab Reimbursement and Use, 127 Ophthalmology 12, 1688–92 (2020).
56 Id.
57 Policy Guideline, United Healthcare Group (UHG), Avastin (Bevacizumab) (Jul. 14, 2021), https://www.uhcpprovider.com/content/dam/provider/docs/public/policies/medadv-guidelines/a/avastin-bevacizumab.pdf, p.4.
Aetna covers bevacizumab and its biosimilars for neovascular AMD. States could benefit from longer term studies examining the impact of private and MAC coverage variability on intravitreal bevacizumab uptake.

Another factor limiting greater off-label bevacizumab use in the USA is the incentive for physicians to prescribe costly treatments under Medicare Part B. Based on the reimbursement formula (ASP plus a percentage markup), prescribers receive a higher dispensing fee for administering drugs with larger ASPs. Studies have shown that increased administration fees drive physician prescribing of expensive drugs. This structure may also undermine the use of lower cost biosimilars of ranibizumab or aflibercept once they arrive to the market. Although changes to Medicare Part B reimbursement rules have been proposed to mitigate these incentives, there are no immediate prospects for reform. Physician preference is also a factor as some studies have suggested better outcomes with aflibercept over bevacizumab and ranibizumab in terms of vision and anatomic outcomes for other conditions. This along with the FDA approval 12 weeks per injection, which could theoretically lead to less treatment burden on patients, may lead many physicians to prefer aflibercept.

A bevacizumab biosimilar would also likely be more rapidly adopted in parts of the world where there is less of a concern regarding feasibility or reliability of widespread compounding. Analyzing the safety of bevacizumab is necessary for a developing country such as India as the majority of the population cannot afford the costly ranibizumab as compared with bevacizumab for ocular healthcare. Thus, both factors—ie compounding and the payment structure of Medicare Part B—combine to dampen the use of intravitreal bevacizumab.

B. Branded Competition and the Power to Negotiate Prescription Drug Prices

Competition between brand-name drugs—in which a new drug is approved within a drug class for the same indication—does not consistently lower drug prices in the USA. It is more common that older drugs influence price setting for new drugs by serving as benchmarks. For example, when aflibercept was approved in 2011, Regeneron set its list price at $1850/dose, while ranibizumab was being sold at $2000/dose. Subsequently, in 2019, Novartis set the list price of brolucizumab at $1850/dose, on a par with aflibercept.

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58 Aetna, Vascular Endothelial Growth Factor Inhibitors for Ocular Indications (June 3, 2021), http://www.aetna.com/cpb/medical/data/700_799/0701.html.

59 Mitchell AP, Winn AN, Dusetzina SB, Pharmaceutical Industry Payments and Oncologists’ Selection of Targeted Cancer Therapies in Medicare Beneficiaries, 178 JAMA Internal Med. 6, 854–6 (2018).

60 Siddiqui M, Rajkumar SV, The High Cost of Cancer Drugs and What We Can Do about It, 87 Mayo Clin. Proc. 10, 935–43 (2012); Kantarjian H et al., High Cancer Drug Prices in the United States: Reasons and Proposed Solutions, 10 J. Oncol. Pract. 4, e208–11 (2014).

61 Wells JA et al., Diabetic Retinopathy Clinical Research Network, Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial, 123 Ophthalmology 6, 1351–9 (Jun. 2016).

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63 Sarpatwari A et al., Competition and Price among Brand-Name Drugs in the Same Class: A Systematic Review of the Evidence, 16 PLOS Med. 7, e1002872 (2019).

64 Pollack A, Success Long in Coming for Eylea, a Vision Treatment (Nov. 20, 2011), https://www.nytimes.com/2011/11/21/business/eylea-a-vision-drug-wins-long-sought-approval.html?ref=health.
One reason for insufficient brand-brand competition is that the USA does not directly negotiate brand-name drug prices. As a result, new brand-name competitors can continue to adhere to high price benchmarks and spending for the health care system does not consistently fall when new brand-name competitors are introduced. In the private US insurance market, prescription drug coverage—often managed by pharmacy benefit managers (PBMs)—involves payors entering into sales contracts with hospitals or pharmacies and setting a formulary of preferentially covered drugs. To attract purchasers, manufacturers may offer rebates on the list price of the drug. These rebates can be used to negotiate more favorable formulary positioning or to facilitate patients’ access to the products. Medicare Part B currently lacks the power to negotiate such rebate agreements.

The contracts and rebate agreements already in place with established biologic manufacturers can make it challenging for newly marketed anti-VEGF biosimilars to gain traction among private payors. For many biologic drugs, such as ranibizumab, agreements have evolved to offer insurers thousands of dollars in rebates each quarter, provided their usage increases from the previous quarter. Certain anti-tumor necrosis factor antibodies have been reported to receive rebates of up to 50 per cent off their list prices. If a manufacturer offers its biosimilar at a substantially discounted price to the payor to match the biologic’s post-rebate price, the originator biologic manufacturer can threaten to withdraw its rebates to payors. With the originator biologic now at its full list price, any patient who continues treatment with it subsequently costs the payer substantially more money. Even if a biosimilar provides a major price discount compared with the brand-name’s post-rebate price, the payor may have to successfully convert most of its patients to the biosimilar treatment to save on overall spending. Otherwise, total payor costs may actually increase relative to costs before biosimilar availability.

This rebate strategy can make it hard for biosimilars to gain traction with private insurers. A recent study found that, out of 535 health plan decisions made by the 17 largest US commercial health plans with publicly available, 14 per cent granted the biosimilar preferred coverage over the reference product, 33 per cent preferred coverage of the reference product over the biosimilar, and 53 per cent did not prioritize either of the two.

C. Biosimilar Interchangeability and a Broken Litigation Pathway?

Besides biosimilars, the BPCIA also introduced the concept of biologic interchangeability. If manufacturers meet additional clinical testing requirements, FDA will designate their biosimilar product as interchangeable, allowing pharmacists to substitute an...
originator biologic automatically for a biosimilar, if state laws allow. Until very recently, there were no interchangeable biosimilars on the market. In 2021, an interchangeable version of the biologic insulin was approved by the FDA, although insulin is a much less complicated biologic than a VEGF inhibitor. Human insulin, for example, consists of only 51 amino acids, while a VEGF inhibitor such as bevacizumab has 214. More interchangeable biosimilars will be made available for US patients when there is sufficient reassurance from the submitted evidence about the safety of automatic substitution.

A second hurdle to overcome for biosimilar manufacturers is the litigation pathway introduced by the BPCIA to resolve biologic patent litigation in a timely fashion. One study highlighted two key factors responsible for the delay in biosimilar launches: failure to comply with steps of the BPCIA litigation process and originator manufacturers enforcing a large number of patents that cover the molecule. A combination of these factors results in confidential settlements satisfactory to the parties, but not to patients who urgently need more affordable medicines to survive. Biosimilar manufacturers may choose not to engage in the process because the sensitive information they have to share in their aBLA is not protected sufficiently and a Supreme Court precedent allows them to avoid this pathway. Add in an extraordinarily large patent thicket covering a biologic molecule that the biosimilar manufacturer must invalidate, and the pathway becomes increasingly less attractive to follow.  

IV. PATHWAYS TO IMPROVE COMPETITION
The prices for anti-VEGF therapies to treat neovascular AMD have been high for many years. Our review of the history and the current market challenges points to a number of potential strategies to achieve effective cost-lowering competition among biologic markets like the one for anti-VEGF therapies. We divided our strategies into two categories: remediying pricing issues and addressing the structural problems with biologic markets.

A. Remediying Pricing Issues
One way to sustain and further increase bevacizumab prescriptions would be to better educate physicians about how cost-conscious prescribing of otherwise clinically identical products can help patients. The AAO website already lists the three main anti-VEGF drugs on the market and deems them to be equally safe and effective treatments. Such efforts would, however, continued to be undermined by the financial incentive physicians have to prescribe more expensive drugs under Medicare Part B.

New payment structures can better leverage cost-effective prescribing. In the case of VEGF inhibitors, that would mean continuing coverage of bevacizumab for neovascular AMD by national pharmaceutical compendia. The federal government can mandate coverage of products under the Social Security Act,” as long as they are published in national compendia (such as the American Hospital Formulary Service Drug Infor-
Competition law and pricing among biologic drugs

Information, National Comprehensive Cancer Network, Biologics Compendium, Drugdex, and Clinical Pharmacology) or have a minimum of at least two articles from major peer-reviewed journals that support the proposed use for the specific medical condition as safe and effective.\textsuperscript{75} States have also enacted legislation preventing private insurance restrictions on anti-cancer drugs. Today, more than three-quarters of all commercially insured patients in the USA reside in states that have passed laws requiring private health insurers to cover off-label uses of cancer drugs similar to Medicare's coverage rules.\textsuperscript{76} Federal or state rules requiring coverage of safely compounded bevacizumab for neovascular AMD among private insurers would help ensure equitable access to the product.

Changes to the clinician reimbursement schedule can also help encourage prescribing of lower cost biosimilars. For example, moderately increasing clinician reimbursement for bevacizumab administration could incentivize prescription rates. One study found a 9 per cent increase in bevacizumab market share in both commercial and Medicare Advantage populations by raising reimbursement to a level that increased the dollar margin to equal that of aflibercept.\textsuperscript{77} Payment for repackaged bevacizumab is governed by the MAC, while aflibercept and ranibizumab are reimbursed based on the ASP. An increase in 2020 bevacizumab reimbursement to $125.78 would equalize the dollar margin over cost with aflibercept in Medicare Part B.\textsuperscript{78} This would eliminate any financial disincentive to use the lower cost drug, which appears to be contributing to lower rates of bevacizumab use. An allowable of $225 that is competitive with commercial carriers would hence still save money under the current model’s assumptions and might increase bevacizumab market share and savings even further.\textsuperscript{79}

A better pathway would be for legislators to reform the aspects of the Medicare Part B reimbursement system. A fixed administration fee, rather than one based on the cost of the underlying product, would reduce incentives to use higher priced drugs. However, this may also lead to less use of potentially more efficacious higher priced drugs in the pipeline such as agents requiring fewer injections or clinic visits leading to lower cost of physician services and less medical risks of frequent treatments on patients as well as reduced indirect costs of patient time, transportation, etc. Another component of the system artificially sustaining high prices is that originator biologics and biosimilars have different payment codes. A single active ingredient-specific payment code would reduce manufacturers’ incentives to price drugs higher than the lowest cost biologic. Such changes would create more savings as it urges physicians to prioritize cost-effectiveness in prescription decisions rather than a higher reimbursement amount for brand-name drugs.\textsuperscript{80}

\textsuperscript{75} American Society of Clinical Oncology, Reimbursement for Cancer Treatment: Coverage of Off-Label Drug Indications, 24 J. Clin. Oncol. 19, 3206–8, (Revised Feb. 27, 2006); Recent Developments in Medicare Coverage of Off-Label Cancer Therapies, 5 J. Oncol. Pract. 1, 18–20 (2009).

\textsuperscript{76} Howard DH et al., Pricing in the Market for Anticancer Drugs, 29 J. Econ. Perspect. 1, 139–62 (2015).

\textsuperscript{77} Id. supra note 12, Glasser et al.

\textsuperscript{78} Id.

\textsuperscript{79} Id.

\textsuperscript{80} Report to the Congress: Medicare and Health Care Delivery System, MedPac, Chapter 3: Part B Drug Payment Policy Issues (June 2015), 61–3, http://www.medpac.gov/docs/default-source/reports/chapte r-3-part-b-drug-payment-policy-issues-june-2015-report-.pdf.
B. Remediying Pricing Issues

Granting Medicare the power to negotiate drug prices with pharmaceutical manufacturers would lead to lower prices for brand-name drugs, including those covered by Medicare Part B.\textsuperscript{81} Legislation that would permit negotiation passed the House of Representatives in December 2019, called the Elijah E. Cummings Lower Drug Costs Now Act.\textsuperscript{82} The bill would provide private insurers with the option of accepting the price negotiated by the government. Although President Trump supported negotiation during his presidential campaign, he abandoned this idea and, in late 2020, proposed tying Medicare Part B drug prices to the cost of the drug in comparable European countries where negotiation is practiced.\textsuperscript{83} While this proposal was subject to litigation from the pharmaceutical industry and has now been taken off the table, President Biden has consistently signaled his support for negotiation, first as a Presidential candidate\textsuperscript{84} and now as President.\textsuperscript{85} Congressional legislation that empowers Medicare to negotiate prices for Part B drugs would trigger much needed savings for the health care system and, more specifically, cut down spending on the most expensive drugs under Part B, including aflibercept and ranibizumab.

In the event that no meaningful Medicare drug spending reform occurs, legislators could pursue a variety of measures. First, legislators could aim to ensure more accurate reporting of ASP data by all manufacturers with products covered in Part B. The Centers for Medicare & Medicaid Services (CMS) perform regular electronic sales price data checks submitted by manufacturers each quarter in search of missing data or incorrect product information. However, CMS does not routinely verify underlying data related to the ASP as reported by manufacturers, which can result in inaccurate Medicare payment rates. CMS also cannot assess all sales price data because only manufacturers with Medicaid drug rebate agreements are required to submit data. The result is that certain payment rates for drugs will be based on incomplete ASP data or will not be set on ASP.\textsuperscript{86}

Second, legislators could revise the Medicare Part B Physician Fee Schedule to group biosimilar and originator biologics under the same reimbursement code. Currently, biosimilars receive their own separate reimbursement codes, while generic drugs are placed within the same reimbursement code as their small-molecule reference products. This administrative distinction does not incentivize physicians to prescribe the cheapest alternative and discourages direct competition between biosimilars and originator biologics. If biosimilars and biologics had the same reimbursement code, they would be more likely to compete with each other, leading to lower prices for patients.

\textsuperscript{81} Hwang TJ et al., Analysis of Proposed Medicare Part B to Part D Shift with Associated Changes in Total Spending and Patient Cost-Sharing for Prescription Drugs, 179 JAMA Intern. Med. 3, 374–80 (2019).
\textsuperscript{82} Elijah E. Cummings Lower Drug Costs Now Act, H.R.3, 116th Congress (2019–20).
\textsuperscript{83} Top of Form Medicare Program; International Pricing Index Model for Medicare Part B Drugs, 83 Fed. Reg. 54546 (Oct. 30, 2018).
\textsuperscript{84} Biden Harris Democrats, Healthcare (last visited Aug. 4, 2021), https://joebiden.com/healthcare/
\textsuperscript{85} Kansteiner F, Biden’s 2022 Budget Re-Ups Prospect of Medicare Drug Pricing Negotiations (June 1, 2021), https://www.fiercepharma.com/pharma/president-biden-s-2022-budget-re-ups-bid-for-medicare-drug-pricing-negotiations.
\textsuperscript{86} U.S. Government Accountability Office (GAO), Medicare Part B: CMS Should Take Additional Steps to Verify Accuracy of Data Used to Set Payment Rates for Drugs (Aug. 1, 2016), https://www.gao.gov/products/gao-16-594.
with reimbursement set to the average price of the clinically similar options, medical practices may be driven to purchase the lowest cost drugs because they would be rewarded by collecting the difference between the average price and the actual purchase price.  

Third, legislators could reduce spending growth by requiring manufacturers to pay Medicare a rebate whenever the ASP increase for their product exceeds an inflation benchmark (to be set by Congress). For example, the Elijah E. Cummings Lower Drug Costs Now Act included this measure. However, the bill would have applied to all drugs, not just originator biologics, and would have used the average manufacturer price to measure drug prices, not the wholesale acquisition cost. Manufacturers that did not pay the requisite rebate amount within 30 days would have been required to pay a penalty equal to 125 per cent of the original rebate amount. Alternatively, Medicare could be authorized to more easily exclude drugs from Part B coverage, which could lead Medicare to favor more inexpensive biosimilar therapies over originator versions.

There is no easy solution to the rebate agreements. With rebate agreements being guarded as trade secrets, it is challenging to determine across the market how well rebates are doing to reduce drug prices to reasonable levels. But as rebates get their power as a negotiation tool from being non-transparent, a system of transparent rebate agreements in the private insurance market could increase the prices of drugs in the long-term. Although rebates are a component of wider drug pricing reform, expensive Anti-VEGFs could specifically benefit from rebate reform. The same is true for proposals to eliminate rebates. For example, in 2018, the Trump administration proposed a rule to remove antikickback safe harbor protection for rebates. Adopting this rule would have moved the biosimilar market to per unit discount-based competition in which individual biologic products would be offered at their best price in exchange for a position on the PBM’s list and, ultimately, the largest market share. However, the rule would shift power in drug pricing negotiations to the manufacturer and it was scored as costing the system money by the Congressional Budget Office. Any changes to the rebate model need to be accompanied by broader changes to the way prices are negotiated in the USA to effectively reduce drug spending.

C. Addressing Structural Problems with Biologic Competition

In the absence of meaningful legislative changes, increased biosimilar competition could also lead to lower prices. In a recent study of seven products that faced biosimilar

87 Conti RM et al., Reform Medicare Part B to Improve Affordability and Equity, Health Affairs Blog (June 25, 2021).
88 Freed M, Cubanski J, Neuman T, A Look at Recent Proposals to Control Drug Spending by Medicare and its Beneficiaries (Nov. 26, 2019), https://www.kff.org/report-section/a-look-at-recent-proposals-to-control-drug-spending-by-medicare-and-its-beneficiaries-issue-brief/
89 42 CFR Part 1001, Fraud and Abuse; Removal of Safe Harbor Protection for Rebates Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection for Certain Point-of-Sale Reductions in Price on Prescription Pharmaceuticals and Certain Pharmacy Benefit Manager Service Fees, https://public-inspection.federalregister.gov/2020-25841.pdf.
90 Congressional Budget Office, Incorporating the Effects of the Proposed Rule on Safe Harbors for Pharmaceutical Rebates in CBO’s Budget Projections—Supplemental Material for Updated Budget Projections: 2019 to 2029 (May 2019), https://www.cbo.gov/system/files/2019-05/55151-SupplementalMaterial.pdf.
competition, the range of 1–3 market entrants for each product resulted in a reduction in weighted average market prices of between 5.4 and 7 percentage points.\textsuperscript{91} Thus, although weaker than in small molecule markets, competitive forces have yielded some price reductions as the number of biosimilar competitors increase. Pfizer (Zirabev) and Amgen (Mvasi) have been predicted to gain a 70 per cent market share in the bevacizumab market with biosimilars by May 2021.\textsuperscript{92} The USA can expect more of these products to reach the market in the near future. While bevacizumab biosimilars will not make a big impact on anti-VEGF pricing standards, biosimilars for ranibizumab and aflibercept have the potential to do so.\textsuperscript{93} Biosimilar competition is poised to drive down spending on anti-VEGFs due to the large anti-VEGF biosimilar pipeline with several candidates in late-stage clinical trials.

Finally, biosimilar manufacturers should continue to conduct additional clinical trials that will sustain their application for interchangeable status from the FDA. Once a product receives interchangeable status, it is easier to substitute for the pharmacist and will therefore see increased uptake. Recent interchangeability designations of insulin glargine (Semglee) and adalimumab-adbm (Cyltezo) confirm the viability of this pathway. Of course, brolucizumab-dbll is a good example of how post-market safety issues can impact use of a drug. As such, future biosimilar competitors to existing anti-VEGF drugs should be closely monitored post-marketing.

V. CONCLUSION
The therapeutic market for age-related neovascular AMD in the USA will likely grow in the next decade. With a patient population expected to double by 2050, a considerable new biosimilar pipeline, and steadily increasing Medicare spending on neovascular AMD therapeutics, new policy initiatives may improve competition and drive down prices. These policies include increasing MAC reimbursement of bevacizumab, adjusting Medicare Part B reimbursement to de-emphasize physician prescription incentives, empowering Medicare to negotiate drug prices, and controlling rebate agreements through broader changes to US pricing system. As biologic patents expire, market access for newer and cheaper biosimilar anti-VEGFs should be facilitated. Robust competition in this therapeutic market will lead to greater savings for the US health care system and, ultimately, ensure patient access to affordable treatments.

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\textsuperscript{91} Frank RG et al., Biosimilar Competition: Early Learning, NBER Working Paper 28460 (Mar. 2021), http://www.nber.org/papers/w28460.
\textsuperscript{92} Adam J. Fein (@DrugChannels), Twitter (Jul. 12, 2021, 1:15 AM), https://twitter.com/DrugChannels/status/1414377728162385922.
\textsuperscript{93} Id. supra note 43; Id. supra note 55.
## APPENDIX: PRODUCTS IN THE ANTI-VEGF PIPELINE AS OF JULY 2021

| Product name | Reference Biologic | Biosimilar or New Product? | Manufacturer | Development Stage |
|--------------|-------------------|----------------------------|--------------|-------------------|
| SB11         | Ranibizumab       | Biosimilar                 | Samsung Bioepis, commercial rights owned by Biogen | Phase III completed |
| SB15         | Afiberecept       | Biosimilar                 | Samsung Bioepis, commercial rights owned by Biogen | Phase III initiated |
| CHS-201      | Ranibizumab       | Biosimilar                 | Coherus Biosciences, licensing agreement with Bioeq | Phase III completed |
| CHS-2020     | Afiberecept       | Biosimilar                 | Coherus Biosciences | Development halted in 2020 |
| PFS82        | Ranibizumab       | Biosimilar                 | Pfenex       | Development halted in 2016 |
| Xlucane      | Ranibizumab       | Biosimilar                 | Xbrane AG    | Phase III initiated  |
| FYB201       | Ranibizumab       | Biosimilar                 | Formycon in collaboration with Bioeq IP AG | Phase III completed |
| ONS-5010     | Bevacizumab       | Biosimilar                 | Outlook Therapeutics | Phase III completed |
| FYB203       | Afiberecept       | Biosimilar                 | Formycon in collaboration with Santo | Phase III initiated |
| MYL-1701P    | Afiberecept       | Biosimilar                 | Mylan Pharmaceuticals | Phase III initiated |
| ALT-L9       | Afiberecept       | Biosimilar                 | Alteogen     | Phase I completed  |
| OPT-302      | Ranibizumab       | Biosimilar                 | Ophthea      | Phase III initiated |
| ABP-938      | Afiberecept       | Biosimilar                 | Amgen        | Phase III initiated |
| Faricimab    |                   | New Reference Product      | Roche (Genentech) | Phase III initiated (TENAYA) ; Phase III initiated (LUCERNE) |
| Abicipar Pegol |                   | New Reference Product      | Allergan     | BLA Accepted by FDA |
| KSI-301      |                   | New Reference Product      | Kodiak Sciences | Phase IIb/III initiated |

*Data collected from statements on company websites and through clinicaltrials.gov.*

95 https://clinicaltrials.gov/ct2/show/record/NCT03150589
96 https://clinicaltrials.gov/ct2/show/NCT04450329
97 https://www.coherus.com/products-and-pipeline/
98 https://www.coherus.com/products-and-pipeline/; https://www.globenewswire.com/en/news-release/2021/05/06/2224975/33333/en/Coherus-BioSciences-Reports-First-Quarter-2021-Financial-Results-and-Immuno-oncology-and-Biosimilar-Pipeline-Progress.html
99 https://www.centerforbiosimilars.com/view/coherus-aims-to-chip-away-at-onpro-dominance
100 https://adisinsight.springer.com/drugs/800038832
101 https://xbrane.com/en/mfn_news/xbrane-biopharma-announces-acceptance-of-initiation-of-xlucane-clinical-trial-in-the-us/
102 https://clinicaltrials.gov/ct2/show/NCT03805100
103 https://www.edisongroup.com/publication/fy18-results-fyb201-launch-on-track-for-2021/24222/
104 https://clinicaltrials.gov/ct2/show/NCT02611778
105 https://clinicaltrials.gov/ct2/show/NCT03844074
106 https://www.edisongroup.com/publication/fy18-results-fyb201-launch-on-track-for-2021/24222/
107 https://clinicaltrials.gov/ct2/show/NCT04522167.
108 http://newsroom.mylan.com/2018-01-03-Momenta-and-Mylan-Announce-Development-Strategy-for-M710-a-Proposed-Biosimilar-to-EYLEA-R-Aflibercept
109 https://clinicaltrials.gov/ct2/show/NCT04674800
