UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC., CELLTRION, INC., and APOTEX, INC.,
Petitioners

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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Case IPR2021-00881[1]
Patent No. 9,254,338 B2

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EXPERT DECLARATION OF RICHARD MANNING, PH.D.

CONFIDENTIAL MATERIAL - SUBJECT TO PROCTECTIVE ORDER

[1] IPR2022-00258 and IPR2022-00298 have been joined with this proceeding.

Summary of Contents

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I, Richard Manning, Ph.D., do hereby declare:

1. Introduction

1.1. Qualifications

(1) I am a Managing Director at Intensity, LLC. I provide data-driven insights to help clients address complex economic questions. Among other things, I have experience conducting economic analyses in matters involving breach of contract, fraud, pricing, economic valuation, intellectual property, antitrust, patent infringement, business strategy, and public policy.

(2) I earned my B.A. in Economics from Brigham Young University. I received my Ph.D. in Economics from the University of Chicago. After obtaining my Ph.D., I was an economics professor at Brigham Young University and a visiting professor in the Graduate School of Business at the University of Chicago. As an academic, my teaching and research focused on price theory, the economic analysis of law, industrial organization, and the economics of government regulation.

(3) My career includes 14 years as an executive at multinational pharmaceutical companies. I was Executive Director at Merck & Co., Inc. and Senior Director at Pfizer, Inc. I led economic analysis and strategy development to shape practices related to emerging business concerns. Examples of my work include:

- Leading and undertaking economic analysis and strategy relative to challenges affecting pricing, reimbursement, and intellectual property protection in global markets.
- Collaborating with outside academic economists to analyze critical issues including healthcare benefit design, healthcare system reform proposals, marketing and advertising, intellectual property protection, FDA regulatory reform, including biosimilars approval processes and safety, and new product R&D.

(4) Previously, I also was a Director in the Advisory Strategy Group at PricewaterhouseCoopers where my responsibilities included working on strategic partnerships, merger and acquisitions activity, economic valuation of early-stage companies, and other economic analyses for biopharmaceutical, medical device, financial, and healthcare clients.

(5) Prior to joining Intensity, I was a Partner at Bates White, an economics consulting firm offering analysis and expert testimony services to law firms, Fortune 500 companies, and government agencies.

(6) My areas of expertise include:

- Economic Valuation and Damages
  - Breach of Contract, Fraud, and other Commercial Litigation
  - Intellectual Property

- Securities Litigation
- Tax, Antitrust and Competition
- Public Policy

(7) I have testified before U.S. District Court, the Delaware Court of Chancery, and the International Chamber of Commerce; served as consulting expert; and prepared reports on various matters in the biopharmaceutical and healthcare industries.

1.2. Scope of work

(8) Intensity has been retained by Arnold & Porter Kaye Scholer LLP on behalf of Regeneron Pharmaceuticals, Inc. (Regeneron). Intensity is being compensated at my standard hourly rate for my work in this matter. Intensity is being compensated for time spent by others on my team at rates lower than my hourly rate. The compensation of Intensity does not depend on the substance of my testimony or the outcome of this matter.

(9) I was asked to evaluate and, if called upon, to testify concerning commercial success as an objective indicia of non-obviousness in *Inter Partes* review No. IPR2021-00881 regarding U.S. Patent No. 9,254,338 (the ’338 Patent).

(10) In forming the opinions expressed in this declaration, I relied upon my education, experience, and knowledge of the subjects discussed. Additionally,

I relied on the declarations of Dr. David M. Brown and Dr. Diana Do. I also have considered documents and other materials, which are cited herein.

(11) In connection with my work in this matter, I have been informed by interviews with the following individuals:

a. Regeneron Director, Customer Insights, interviewed on November 30th, 2021.

b. Regeneron Associate Director, Field Force Effectiveness and Ophthalmology, and Regeneron Associate Director, Sample Operations and Accountability, interviewed on December 15th, 2021.

c. Regeneron Executive Director, Commercial Finance & Business Planning and Regeneron Senior Director, FP&A, interviewed on December 16th, 2021.

d. Regeneron Senior Director, Market Access Strategy, interviewed on February 9th, 2022.

1.3. Framework for commercial success

(12) I understand that evidence of commercial success is one of the objective indicia that a patent owner may rely upon to support an argument of non-

obviousness of a claimed invention.[2] I understand that the Federal Circuit has stated that "[c]ommercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art."[3] I understand that, for commercial success to constitute evidence of non-obviousness of a patent, there must be a nexus between the claimed technology and evidence of commercial success, and that the evidence must demonstrate that the commercial success is due at least in part to the claimed features of the invention and not to factors unrelated to the claimed invention.[4] I further

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2 *Demaco Corp. v. F. Von-Langsdorff Licensing Ltd.*, 851 F.2d 1387, at PDF 3 (Fed. Cir. 1988).

3 *Merck v. Teva*, 395 F.3d 1364, 1376 (Fed. Cir. 2005).

4 United States Patent and Trademark Office, Manual of Patent Examining Procedure, Eighth Edition, Revision: 7/2010, 716.03 I., at 700-298. ("An applicant who is asserting commercial success to support its contention of nonobviousness bears the burden of proof of establishing a nexus between the claimed invention and evidence of commercial success.") ("The term "nexus" designates a factually and legally sufficient connection between the evidence

understand that Federal Circuit case law holds that "if the commercial success is due to an unclaimed feature or device, the commercial success is irrelevant."[5]

(13) It is my understanding that the courts commonly accept indicators including significant sales levels, significant sales growth, substitution towards the

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of commercial success and the claimed invention so that the evidence is of probative value in the determination of nonobviousness.") ("In considering evidence of commercial success, care should be taken to determine that the commercial success alleged is directly derived from the invention claimed, in a marketplace where the consumer is free to choose on the basis of objective principles, and that such success is not the result of heavy promotion or advertising, shift in advertising, consumption by purchasers normally tied to applicant or assignee, or other business events extraneous to the merits of the claimed invention, etc.")

Demaco Corp. v. F. Von-Langsdorff Licensing Ltd., 851 F.2d 1387, at PDF 3 (Fed. Cir. 1988).

5 *Ormco Corporation, et al. v. Align Technology, Inc., 463 F.3d 1299, 1312 (Fed. Cir. 2006)*.

novel product or method and away from alternative products or methods, price premiums, or the absence of substantial discounting, and other economic indicators as evidence of commercial success of a novel product.[6] In the context of pharmaceutical products (and by extension biologic products), sales can be measured in terms of revenues, prescriptions, or daily doses, and sales growth can be measured in terms of sales or share of sales within a product category.[7]

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[6] Ex. 2201 (Guha, Rahul, Jian Li, and Andrea L. Scott (2009), "The Economics of Commercial Success in Pharmaceutical Patent Litigation," *Landslide* 1(5)).

[7] Ex. 2201 (Guha (2009)).

2. Regeneron Pharmaceuticals, Inc.

(14) Regeneron Pharmaceuticals, Inc. (Regeneron) is a biotechnology company that discovers and develops biotherapeutics for people with serious illnesses.[8] Regeneron was incorporated in the state of New York in 1988 and has its corporate headquarters is in Tarrytown, New York.[9] Regeneron was publicly listed on NASDAQ in 1991.[10]

(15) The company's approved therapeutic products and its therapeutic candidates in development target eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, pain, infectious diseases, and other rare diseases.[11] Regeneron's portfolio includes "over 30 investigational medicines."[12]

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[8] Ex. 2246 (Regeneron Website, About, https://www.regeneron.com/about (accessed 11/3/2021)).

[9] Ex. 2254 (Regeneron, Form 10-K, 2020, at 37).

[10] Ex. 2254 (Regeneron, Form 10-K, 2020, at 37).

[11] Ex. 2254 (Regeneron, Form 10-K, 2020, at 3).

[12] Ex. 2253 (Regeneron Website, Research Areas, https://www.regeneron.com/science/research-areas (accessed 11/3/2021)).

(16) In 2011, the FDA approved Regeneron's EYLEA (aflibercept) injection for the treatment of wet age-related macular degeneration (wet AMD).[13] EYLEA is a prescription medicine approved for the treatment of patients with a variety of angiogenic eye diseases and is the subject of this proceeding.[14]

[13] Ex. 2251 (Regeneron Website, History, https://www.regeneron.com/about/history (accessed 12/15/2021)).

Ex. 2185 (Drugs@FDA, Eylea Label, 11/2011, at 1, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf).

[14] Ex. 2254 (Regeneron, Form 10-K, 2020, at 3).

3. U.S. Patent No. 9,254,338

(17) U.S. Patent No. 9,254,338, entitled "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders," was issued on February 9, 2016.[15] The '338 Patent lists George D. Yancopoulos as its inventor and Regeneron Pharmaceuticals, Inc. as its assignee.[16] The '338 Patent claims a priority date of January 13, 2011, and the application resulting in the '338 Patent was filed on July 12, 2013.[17]

(18) The abstract of the '338 Patent reads as follows:[18]

> The present invention provides methods for treating angiogenic eye disorders by sequentially administering multiple doses of a VEGF antagonist to a patient. The methods of the present invention include the administration of multiple doses of a VEGF antagonist to a patient at a frequency of once every 8 or more weeks. The methods of the present invention are useful for the treatment of angiogenic eye disorders such as age-related

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15 Ex. 1001 (Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders, U.S. Patent No. 9,254,338 (filed 7/12/2013, issued 2/9/2016)).

16 Ex. 1001 (U.S. Patent No. 9,254,338).

17 Ex. 1001 (U.S. Patent No. 9,254,338).

18 Ex. 1001 (U.S. Patent No. 9,254,338).

macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

(19) The ’338 Patent has 26 claims.[19] Of these 26 claims, 22 are currently under review in this proceeding: claims 1, 3-11, 13, 14, 16-24, and 26.[20] Generally, I understand that the ’338 Patent teaches the use of a VEGF antagonist made from specific amino acid sequences or a specific nucleic acid sequence to treat angiogenic eye disorders according to a dosing regimen that includes three phases: a single initial dose; one or more secondary doses administered 2 to 4 weeks after the preceding dose; and one or more tertiary doses administered at least 8 weeks after the preceding dose.[21]

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19 Ex. 1001 (U.S. Patent No. 9,254,338).

20 Decision Granting Institution of *Inter Partes* Review, 11/10/2021, at 2.

21 Ex. 1001 (U.S. Patent No. 9,254,338).

Ex. 2050 (Expert Declaration of David M. Brown, M.D. (“Brown Declaration”), 2/10/2022. at ¶94). (“The dosing regimen of Claim 1 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more “secondary” doses

(20) I understand that Eylea is administered according to the claimed dosing regimen.[22] For example, the FDA approved label for Eylea for wet AMD recommends a monthly injection for the first three to five months, depending on the indication, followed by an on-going 8-week or longer maintenance dosing schedule.[23] I will refer to these initial monthly doses (i.e., the single

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administered two to four weeks after the preceding dose, and then one or more "tertiary" doses that are administered at least eight weeks following the preceding dose.

Ex. 2051 (Declaration of Diana V. Do, M.D. ("Do Declaration"), 2/10/2022, at ¶35). ("The dosing regimen of Claim 1 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more "secondary" doses administered two to four weeks after the preceding dose, and then one or more "tertiary" doses that are administered at least eight weeks following the preceding dose.")

[22] Ex. 2051 (Do Declaration, 2/10/2022, at ¶¶ 135–139).

[23] Ex. 2189 (Drugs@FDA, Eylea Label, 3/2021, at 3, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125387s069lbl.pdf). ("The recommended dose for EYLEA is 2 mg (0.05 mL) administered by

initial dose and the one or more secondary doses administered 2 to 4 weeks after the preceding dose) as the "loading doses" or loading period, and tertiary doses as the "maintenance doses" or maintenance phase.

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intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).")

4. Relevant Economic Principles

(21) The economic theory of demand dictates that consumers choose to buy goods and services to achieve satisfaction, or to meet various wants and needs.[24] Demand theory also dictates that consumers only buy things when the good purchased provides them greater value than the cost they incur to acquire the good.[25] The cost incurred includes more than the money paid.[26]

(22) As a consumer evaluates a purchase, he or she considers other things that are "bundled" with the purchase, and, importantly, a consumer considers the

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[24] Ex. 2219 (Mankiw, Nicholas Gregory (2009), *Principles of Microeconomics*, 5th ed., Mason, OH: South-Western Cengage Learning, at 6). ("You will also encounter individuals who decide how much time to spend working and what goods and services to buy with the resulting income to achieve the highest possible level of satisfaction.")

[25] Ex. 2219 (Mankiw (2009), at 5). ("Because people face trade-offs, making decisions requires comparing the costs and benefits of alternative courses of actions.")

[26] Ex. 2219 (Mankiw (2009), at 5). ("In many cases, however, the cost of an action is not as obvious as it might appear.")

alternative consumption opportunities that are given up in exchange for the purchased good.[27] Within the consumption bundle, the consumer may find things both good and bad that contribute to the "price" paid in exchange for the thing he or she wants to buy. When a consumption bundle includes bad things, demand for the bundle is diminished.[28]

(23) In this matter, the medical treatments provide significant benefits and value to patients by preventing vision loss and restoring some lost vision caused by the relevant medical conditions. However, as discussed subsequently in my declaration, the most commonly used treatments for these conditions (including Eylea) involve ongoing treatments, which impose certain "bads" on patients. See Section 9. In particular, these treatments are administered by injection into patients' eyes, compounding the negative impact of ongoing

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[27] Ex. 2219 (Mankiw (2009), at 5–6). ("The **opportunity cost** of an item is what you give up to get that item. When making any decision, decision makers should be aware of the opportunity costs that accompany each possible action.")

[28] Ex. 2245 (Pindyck, Robert and Daniel Rubinfeld (2013), *Microeconomics*, Upper Saddle River, NJ: Prentice Hall, at 76-77). ("However, some things are **bads**: *Less of them is preferred to more*.")

treatment.[29] Hence, economic theory indicates, all else the same, that a treatment that requires fewer or less frequent doses and/or evaluations will be in greater demand by consumers than is a treatment that requires more evaluations, and/or more frequent dosing.

[29] Ex. 2221 (Mayo Clinic Website, Wet Macular Degeneration, https://www.mayoclinic.org/diseases-conditions/wet-macular-degeneration/diagnosis-treatment/drc-20351113 (accessed 11/11/2021)).

5. Medical Conditions at Issue

(24) The ’338 Patent teaches “methods for treating angiogenic eye disorders.”[30] I understand that angiogenic eye disorders result from the growth of abnormal blood vessels in the eyes[31] when a naturally-produced protein, vascular endothelial growth factor (VEGF), is produced in excess amounts. The creation of these abnormal blood vessels in eyes can damage the eye and impair vision.[32]

(25) The ’338 Patent specifically identifies the patented methods as being useful for the treatment of specific angiogenic eye disorders, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.[33] Of these, Eylea has obtained FDA approval for use

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30 Ex. 1001 (U.S. Patent No. 9,254,338).

31 Ex. 2179 (Dreyfuss, Juliana L., Ricardo J. Giordano, and Caio V. Regatieri (2015), “Ocular Angiogenesis,” *Journal of Ophthalmology* 2015:892043).

The formation of new blood vessels is labeled angiogenesis.

32 Ex. 2050 (Brown Declaration, 2/10/2022, at ¶ 26).

33 Ex. 1001 (U.S. Patent No. 9,254,338).

treating four angiogenic eye disorders: wet AMD, diabetic retinopathy (DR), diabetic macular edema (DME), and retinal vein occlusion (RVO).[34]

(26) Detailed descriptions of each of the angiogenic eye disorders at issue in this matter can be found from sites including the American Society of Retina Specialists (ASRS).[35] Across the diseases at issue, the majority of anti-VEGF

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[34] Ex. 2185 (Eylea Label, 11/2011, at 1).

Ex. 2187 (Drugs@FDA, Eylea Label, 10/2014, at 4, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf).

Ex. 2188 (Drugs@FDA, Eylea Label, 5/2019, at 4, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125387s061lbl.pdf).

[35] Ex. 2149 (American Society of Retina Specialists Website, Age-Related Macular Degeneration, https://www.asrs.org/patients/retinal-diseases/2/agerelated-macular-degeneration (accessed 12/30/2021)).

Ex. 2152 (American Society of Retina Specialists Website, Diabetic Retinopathy, https://www.asrs.org/patients/retinal-diseases/3/diabetic-retinopathy (accessed 12/30/2021)).

injections regardless of type are used on patients with wet AMD and DME. See Table 1. Indeed, 83.5% of all anti-VEGF injections are used on patients with either wet AMD or DME. See Table 1.

Ex. 2182 (Elyasi, Niki and Houman David Hemmati (2021), "Diabetic Macular Edema: Diagnosis and Management," *EyeNet Magazine*, May 2021: 35-37).

Ex. 2151 (American Society of Retina Specialists Website, Central Retinal Vein Occlusion, https://www.asrs.org/patients/retinal-diseases/22/central-retinal-vein-occlusion (accessed 12/30/2021)).

Ex. 2150 (American Society of Retina Specialists Website, Branch Retinal Vein Occlusion, https://www.asrs.org/patients/retinal-diseases/24/branch-retinal-vein-occlusion (accessed 12/30/2021)).

Table 1: U.S. Anti-VEGF Injections by Relevant Disease in 2021[36]

Disease	Total Injections	Percent of Total Injections
Wet AMD	[redacted]	[redacted]
DME	[redacted]	[redacted]
DR without DME	[redacted]	[redacted]
RVO	[redacted]	[redacted]

(27) Generally speaking, these diseases tend to afflict individuals who are age 50 or older. For example, wet AMD is most common in people aged 55 or older.[37]

[36] Ex. 2273 (Vestrum, Anti-VEGF Category Sales Shares, c. 2/2022, at tab "Eylea – Quarterly by Indication").

[37] Ex. 2222 (Mayo Clinic Website, Wet Macular Degeneration Symptoms and Causes, https://www.mayoclinic.org/diseases-conditions/wet-macular-degeneration/symptoms-causes/syc-20351107 (accessed 11/11/2021)).

Additional sources discussing the age at which wet AMD appears:

Similarly, the average age at patients' diagnosis of DME is "just over 50 years old."[38]

Ex. 2164 (Bright Focus Foundation Website, Age-Related Macular Degeneration: Facts & Figures, https://www.brightfocus.org/macular/article/age-related-macular-facts-figures (accessed 11/5/2021)). ("Macular degeneration is a leading cause of vision loss in Americans 60 years of age and older.")

Ex. 2264 (Verywell Health Website, Macular Degeneration: Timeline of Vision Loss Progression, 3/21/2021, https://www.verywellhealth.com/macular-degeneration-timeline-5069947). ("Age-related macular degeneration usually begins at age 55 or older.")

Ex. 2183 (Eye Care Surgery Center Website, Macular Degeneration, https://www.eyecaresurgerycenterbr.com/diabetes-retina/macular-degeneration/ (accessed 11/18/2021)). ("It [wet AMD] rarely occurs before the age of 50.")

[38] Ex. 2262 (Sivaprasad, Sobha (2021), "Sustained-Release Steroid Options For DME Therapy," *Retina Today* (0921): 34–36, at 34).

(28) These angiogenic eye disorders are treated by ophthalmologists, either retinal specialists or comprehensive ophthalmologists.[39] As of 2016, there were over 17,000 ophthalmologists in the U.S., with 3,329 identified as retina providers.[40] Of these 3,329 retina providers, 1,034 were identified as

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[39] Ex. 2141 (American Academy of Ophthalmology Website, Anti-VEGF Treatments, https://www.aao.org/eye-health/drugs/anti-vegf-treatments (accessed 11/8/2021)).

Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 3).

Regeneron's ATU surveys are conducted for retinal specialists and general ophthalmologists that administer the anti-VEGF treatments through intravitreal injection.

Conversation with Regeneron Director, Customer Insights.

[40] Ex. 2203 (Healio, "Access to Retina Providers Shows No Geographic Bias in U.S.," 3/12/2019, at 1, available at: https://www.healio.com/news/ophthalmology/20190312/access-to-retina-providers-shows-no-geographic-bias-in-us).

Ex. 2148 (American Society of Retina Specialists Website, About Us. https://www.asrs.org/about (accessed 12/6/2021)).

comprehensive providers or hybrid providers (physicians that diagnose and treat a broad array of eye diseases); the remaining 2,295 were identified as retina specialists (ophthalmologists with additional intensive training through a fellowship that focused on the retina).[41]

[41] Ex. 2203 (Healio, "Access to Retina Providers Shows No Geographic Bias in U.S.," 3/12/2019, at 1).

Ex. 2148 (American Society of Retina Specialists Website, About Us. https://www.asrs.org/about (accessed 12/6/2021)).

Ex. 2143 (American Academy of Ophthalmology, "Ophthalmology Subspecialists," 6/6/2016, https://www.aao.org/eye-health/tips-prevention/ophthalmology-subspecialists).

6. Overview of Treatment Options for Relevant Angiogenic Eye Disorders

(29) Various options have been or are currently used by physicians for treatment of angiogenic eye disorders, with different treatment options available for each disorder. Eylea and other anti-VEGF therapies are now the most common treatment for angiogenic eye diseases.[42] See Attachment C-1. A more in-depth discussion of these treatments can be found in the Brown Declaration.[43]

6.1. Laser-based treatment options available prior to anti-VEGF therapies

(30) In addition to other medicines no longer in common use, early treatments for wet AMD included the use of lasers applied to the retina. Laser photocoagulation, also known as laser ablation, was an early treatment option

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[42] Ex. 2271 (Yorston, David (2014), "Anti-VEGF Drugs in the Prevention of Blindness," *Community Eye Health Journal* 27(87): 44-47, at 47). ("In summary, anti-VEGF drugs are probably the most significant advance in ophthalmology in the last decade. They have enabled us to treat what were previously untreatable conditions.")

[43] Ex. 2050 (Brown Declaration, 2/10/2022, at ¶¶ 26–69).

for wet AMD and DR, dating back to the 1970s.[44] This treatment involved the use of a laser to create microscopic burns in target tissue to stop new blood vessels from growing in the eye.[45] In 2000, the FDA granted approval to treat wet AMD using photodynamic therapy. In photodynamic therapy, or PDT, the drug Visudyne is injected into the patient's arm and a laser is used to activate the injected drug in the patient's eye.[46] Generally, I understand that

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[44] Ex. 2255 (Retinal Physician, "Revisiting an Early Treatment for Wet AMD: Is There a Role for Thermal Laser in the Era of Anti-VEGF Therapy?" 9/1/2011, https://www.retinalphysician.com/issues/2011/september-2011/revisiting-an-early-treatment-for-wet-amd).

[45] Ex. 2228 (Medline Plus Website, Laser Photocoagulation – Eye, https://medlineplus.gov/ency/article/007664.htm (accessed 12/2/2021)).

Ex. 2050 (Brown Declaration, 2/10/2022, at ¶¶ 27–28).

[46] Ex. 2267 (Drugs@FDA, Visudyne Label, 4/2016, at 3, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021119s027lbl.pdf).

Ex. 2158 (Bausch and Lomb Website, Visudyne, https://www.bauschretinarx.com/visudyne/ecp/about/ (accessed 12/2/2021)).

these laser-based treatments were able to slow or prevent further vision loss for some patients, but they did not help patients recover vision.[47]

6.2. Anti-VEGF treatment options

(31) Since the mid-2000s, anti-VEGF products have become the primary treatment for angiogenic eye disorders.[48] Anti-VEGF treatments are administered by

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Ex. 2159 (Bausch and Lomb Website, Help Your Patients Obtain Access to Visudyne, https://www.bauschretinarx.com/visudyne/ecp/ordering/ (accessed 1/12/2022)).

Ex. 2204 (Hopkins Medicine Website, Photodynamic Therapy for Age-Related Macular Degeneration, https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/photodynamic-therapy-for-agerelated-macular-degeneration (accessed 12/2/2021)).

47 Ex. 2050 (Brown Declaration, 2/10/2022, at ¶ 28).

48 Ex. 2271 (Yorston (2014), at 46). ("In summary, anti-VEGF drugs are probably the most significant advance in ophthalmology in the last decade. They have enabled us to treat what were previously untreatable conditions.")

injection into patients' eyes.[49] These treatments have included the following products.

6.2.1. Macugen

(32) In December 2004, the FDA approved Macugen (the brand name for pegaptanib) for the treatment of wet AMD.[50] Macugen is an anti-VEGF aptamer (a single strand DNA or RNA molecule that binds to specific targets) developed by Eyetech Pharmaceuticals and Pfizer.[51] I understand that

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[49] Ex. 2221 (Mayo Clinic Website, Wet Macular Degeneration (accessed 11/11/2021)).

[50] Ex. 2191 (FDA, "Macugen Drug Approval Package Page," 3/23/2005, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-756_Macugen.cfm).

Ex. 2217 (Drugs@FDA, Macugen Label, 12/2004, at 4, 8, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/021756lbl.pdf).

[51] Ex. 2217 (Macugen Label, 12/2004, at 4, 5, 11).

Ex. 2157 (BasePair Biotechnologies Website, What is an Aptamer? – Aptamers and SELEX, https://www.basepairbio.com/what-is-an-aptamer/ (accessed 12/30/2021)).

Macugen was more effective at slowing continued vision loss than prior treatments, but that it did not stop or restore vision loss.[52]

6.2.2. Avastin

(33) Avastin is the brand name for the antibody bevacizumab, which was developed by Genentech (a member of the Roche group) and initially approved by the FDA in February 2004 as a treatment for metastatic colorectal cancer.[53] Beginning in 2005, however, Avastin began to be used as an off-label treatment for wet AMD, diabetic eye disease, and other problems of the

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[52] Ex. 2050 (Brown Declaration, 2/10/2022, at ¶ 30).

[53] Ex. 2261 (ScienceDaily, "FDA Approves First Angiogenesis Inhibitor to Treat Colorectal Cancer," 2/27/2004, https://www.sciencedaily.com/releases/2004/02/040227071334.htm).

Ex. 2156 (Drugs@FDA, Avastin Label, c. 2004, at 2, 7, 27, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf).

retina.[54] I understand that in some patients Avastin use results in restoration of some of the vision losses from angiogenic eye disorders.[55]

6.2.3. Lucentis

(34) Lucentis is the brand name for ranibizumab, an antibody fragment designed to block VEGF inside the eye.[56] Lucentis was developed by Genentech and

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[54] Thomas Albini, Dep Tr., 1/20/2022, at 29:17–18.

Ex. 2145 (American Academy of Ophthalmology, "What is Avastin", 4/3/2021, https://www.aao.org/eye-health/drugs/avastin).

Avastin is not approved by the FDA for the treatment of wet AMD or any angiogenic eye disorders. See:

Ex. 2142 (American Academy of Ophthalmology, "Bevacizumab," 11/2/2021, https://eyewiki.aao.org/Bevacizumab.)

[55] Ex. 2050 (Brown Declaration, 2/10/2022, at ¶ 40).

[56] Ex. 2147 (American Academy of Ophthalmology, "What is Lucentis", 4/26/2021, https://www.aao.org/eye-health/drugs/lucentis).

Ex. 2212 (Drugs@FDA, Lucentis Label, c. 2006, at 4, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/125156lbl.pdf).

received FDA approval for treatment of wet AMD in June 2006.[57] Lucentis has since been approved to treat patients with macular edema following RVO (June 2010), DME (August 2012), and DR (April 2017).[58] I understand that

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[57] Ex. 2199 (Genentech Press Release, "FDA Approves Lucentis for the Treatment of Wet Age-Related Macular Degeneration," 6/30/2006, https://www.roche.com/dam/jcr:4ca7683d-1513-4e46-bd43-23faa0232507/en/irp060703.pdf).

Ex. 2212 (Lucentis Label, c. 2006, at 1).

[58] Ex. 2198 (GEN, "FDA Green-Lights Genentech's Lucentis for Macular Edema following Retinal Vein Occlusion," 6/23/2010, https://www.genengnews.com/news/fda-green-lights-genentechs-lucentis-for-macular-edema-following-retinal-vein-occlusion/).

Ex. 2257 (Roche Press Release, "FDA Approves Lucentis for Treatment of Diabetic Macular Edema," 8/13/2012, https://www.roche.com/investors/updates/inv-update-2012-08-13.htm).

Ex. 2258 (Roche Press Release, "FDA Approves Roche's Lucentis for Diabetic Retinopathy, the Leading Cause of Blindness Among Working Age

Lucentis administration can allow patients to regain some of the vision losses from angiogenic eye disorders.[59]

6.2.4. Eylea

(35) Eylea is the brand name of the biologic aflibercept, an anti-VEGF fusion protein developed by Regeneron Pharmaceuticals.[60] Eylea was approved for

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Adults in the United States, 4/18/2017, https://www.roche.com/media/releases/med-cor-2017-04-18b.htm).

Ex. 2213 (Drugs@FDA, Lucentis Label, 6/2010, at 5, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125156s053lbl.pdf).

Ex. 2214 (Drugs@FDA, Lucentis Label, 8/2012, at 6, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125156s0069s0076lbl.pdf).

[59] Ex. 2050 (Brown Declaration, 2/10/2022, at ¶ 40).

[60] Ex. 2146 (American Academy of Ophthalmology, "What is Eylea", 4/23/2021, https://www.aao.org/eye-health/drugs/what-is-eylea).

Ex. 2185 (Eylea Label, 11/2011, at 9, 15).

the treatment of wet AMD in November of 2011.[61] Eylea has also been approved for treatment of DME (July 2014), RVO (initially in September 2012 for CRVO, expanded in October 2014), and general DR (May 2019).[62]

A fusion protein is an engineered molecule that incorporates the genes of two proteins and has an enhanced ability to treat disease. See:

Ex. 2153 (Amgen Website, Fusion Protein, https://www.amgen.com/stories/2018/08/the-shape-of-drugs-to-come/fusion-protein (accessed 1/7/2022)).

[61] Ex. 2185 (Eylea Label, 11/2011, at 1).

[62] Ex. 2247 (Regeneron Press Release, "Eylea Injection Receives FDA Approval for the Treatment of Diabetic Macular Edema (DME)," 7/29/2014, https://investor.regeneron.com/news-releases/news-release-details/eylear-aflibercept-injection-receives-fda-approval-treatment).

Ex. 2252 (Regeneron Press Release, "Regeneron Announces FDA Approval of Eylea Injection for Macular Edema Following Central Retinal Vein Occlusion," 9/21/2012, https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-fda-approval-eylear-aflibercept-injection).

Most recently in 2019, Eylea was approved to treat patients with any stage of DR.[63] As with Lucentis and Avastin, I understand that Eylea administration can assist patients to regain some of the vision losses from angiogenic eye disorders.[64]

Ex. 2248 (Regeneron Press Release, "Eylea Injection Receives FDA Approval for Macular Edema Following Retinal Vein Occlusion (RVO)," 10/6/2014, https://investor.regeneron.com/news-releases/news-release-details/eylear-aflibercept-injection-receives-fda-approval-macular-edema).

Ex. 2249 (Regeneron Press Release, "FDA Approves Eylea Injection for Diabetic Retinopathy", 5/13/2019, https://investor.regeneron.com/news-releases/news-release-details/fda-approves-eylear-aflibercept-injection-diabetic-retinopathy).

Ex. 2187 (Eylea Label, 10/2014, at 4).

63 Ex. 2188 (Eylea Label, 5/2019, at 4).

64 Ex. 1001 (U.S. Patent No. 9,254,338, Example 4).

6.2.5. Beovu

(36) Beovu is the brand name for the biologic brolucizumab, an antibody fragment and VEGF inhibitor introduced by Novartis.[65] The FDA approved Beovu in vial form in October 2019 to treat patients with wet AMD.[66] At the time, it was the only anti-VEGF product to offer possible vision maintenance for wet

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[65] Ex. 2161 (Drugs@FDA, Beovu Label, 10/2019, at 7, 14, 18, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf).

[66] Ex. 2231 (Novartis Press Release, "Novartis Receives FDA Approval for Beovu, Offering Wet AMD Patients Vision Gains and Greater Fluid Reductions vs Aflibercept," 10/8/2019, https://www.novartis.com/news/media-releases/novartis-receives-fda-approval-beovu-offering-wet-amd-patients-vision-gains-and-greater-fluid-reductions-vs-aflibercept).

Ex. 2161 (Beovu Label, 10/2019, at 7, 18).

AMD patients using a three-month dosing interval following a loading phase of three injections administered monthly.[67]

(37) Although Beovu had initial success, safety concerns arose regarding vision loss associated with the product. In February 2020, the American Society of Retina Specialists issued a note to members informing them of cases of retinal vasculitis in Beovu patients.[68] Four months later, Novartis revised Beovu's label to include the newly established risk. The FDA approved the new label

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[67] Ex. 2231 (Novartis Press Release, "Novartis Receives FDA Approval for Beovu, Offering Wet AMD Patients Vision Gains and Greater Fluid Reductions vs Aflibercept," 10/8/2019).

Ex. 2161 (Beovu Label, 10/2019, at 7).

[68] Ex. 2193 (FiercePharma, "Novartis' Hot New Eye Drug Beovu Tied to Potential Vision Loss: Experts," 2/24/2020, https://www.fiercepharma.com/pharma/retinal-society-flags-serious-side-effect-for-novartis-beovu).

Retinal vasculitis is the inflammation of retinal blood vessels. See:

Ex. 2144 (American Academy of Ophthalmology Website, Retinal Vasculitis, https://eyewiki.aao.org/Retinal_Vasculitis (accessed 1/13/2022)).

in June 2020.[69] Beovu's revised label added expanded "warnings and precautions" to include retinal vasculitis and RVO,[70] both of which can result in permanent vision loss.[71] Further, these new side effects do not apply to other

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[69] Ex. 2232 (Novartis Press Release, "US FDA Approves Updated Novartis Beovu Label, to Include Additional Safety Information," 6/11/2020, https://www.novartis.com/news/media-releases/us-fda-approves-updated-novartis-beovu-label-include-additional-safety-information).

[70] See changes to the warnings and precautions between the two labels:

Ex. 2162 (Drugs@FDA, Beovu Label, 6/2020, at 3, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761125s004lbl.pdf).

Ex. 2161 (Beovu Label, 10/2019, at 7).

[71] Ex. 2180 (Miller & Zois, LLC, "Novartis Looking to Repurpose its Dangerous Beovu Drug," 11/28/2020, https://www.drugrecalllawyerblog.com/novartis-repurpose-beovu.html).

available anti-VEGF treatments.[72] Ophthalmologists may have hastened their disuse of Beovu because Covid-19 related shutdowns made it difficult for physicians to undertake recommended post-administration monitoring of patients following Beovu injections, and as a result, Beovu utilization has fallen substantially.[73] According to data from Vestrum, Beovu's sales share peaked at ~2.5% in 2020-Q1, two quarters after its launch in 2019-Q3. See Attachment X-1. The sales share began declining in 2020-Q2 and Q3, which

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[72] Unlike the Beovu label, the warnings and precautions on the labels for Eylea and Lucentis do not list retinal vasculitis nor retinal vascular occlusion. See:

Ex. 2189 (Eylea Label, 3/2021, at 3).

Ex. 2216 (Drugs@FDA, Lucentis Label, 3/2018 at 4, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125156s117lbl.pdf).

Ex. 2193 (FiercePharma, "Novartis' Hot New Eye Drug Beovu Tied to Potential Vision Loss: Experts," 2/24/2020).

[73] Ex. 2192 (FiercePharma, "Beovu, Novartis," 10/25/2021, https://www.fiercepharma.com/special-report/beovu-novartis-top-10-drug-launch-disasters).

corresponds with the timing of the new warnings on the label. Beovu's sales share in 2021-Q3 was ~0.7%. See Attachment X-1.

6.2.6. FDA approvals for anti-VEGF treatments

(38) Table 2 contains the FDA approval dates, if applicable, for the 5 anti-VEGF treatment options (Macugen, Avastin, Lucentis, Eylea, and Beovu).

Table 2: FDA Approval Dates[74]

Treatment	Wet AMD	RVO	DME	DR
Macugen	Dec. 2004	n/a	n/a	n/a
Avastin	Off-label	Off-label	Off-label	Off-label
Lucentis	Jun. 2006	Jun. 2010	Aug. 2012	Apr. 2017
Eylea	Nov. 2011	Sep. 2012	Jul. 2014	May 2019
Beovu	Oct. 2019	n/a	n/a	n/a

[74] For Macugen See Section 6.2.1

For Avastin See Section 6.2.2

For Lucentis See Section 6.2.3

For Eylea See Section 6.2.4

6.2.7. FDA-approved dosing schedules for anti-VEGF treatment options

(39) Three of the anti-VEGF treatment options used for diseases of the retina (Eylea, Lucentis, and Beovu) have a recommended dosing schedule on their FDA approved labels.[75] Avastin is used off-label for the treatment of retinal disease and as such does not have an FDA approved label for these uses.[76] The FDA approved label for each of the three products recommends monthly loading injections for the first three to five months, depending on the indication, followed by an on-going maintenance dosing schedule.[77]

For Beovu See Section 6.2.5

75 Ex. 2189 (Eylea Label, 3/2021, at 3).

Ex. 2216 (Lucentis Label, 3/2018, at 4).

Ex. 2162 (Beovu Label, 6/2020, at 3).

76 Recall that treatment of retinal diseases with Avastin is "off-label". See Section 6.2.2.

77 For example, Eylea's directions for wet AMD state: "The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4

(40) Following the loading period, each of the three FDA approved treatments has a different recommended dosing interval depending upon the indication. Table 3 below summarizes the recommended dosing intervals. See Attachment B-1.

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weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)."

Ex. 2189 (Eylea Label, 3/2021, at 3).

Ex. 2216 (Lucentis Label, 3/2018, at 4).

Ex. 2162 (Beovu Label, 6/2020, at 13).

Table 3: Recommended and Maximum Dosing in Maintenance Phase[78]

Condition[79]	Eylea	Lucentis	Beovu[80]
Wet AMD (Recommended)	8 weeks	4 weeks	8 to 12 weeks
Wet AMD (Maximum)	12 weeks	12 weeks	8 to 12 weeks
DME	8 weeks	4 weeks	n/a
DR	8 weeks	4 weeks	n/a
RVO	4 weeks	4 weeks	n/a

(41) For wet AMD, DME, and DR, Eylea's recommended dosing interval of 8 weeks is longer than Lucentis' recommended dosing interval of 4 weeks. For the treatment of wet AMD only, the FDA labels for Eylea and Lucentis also

78 Avastin omitted as there is no approved label for the relevant conditions.

79 Eylea and Lucentis labels contain different recommended dosing intervals and maximum dosing intervals for the maintenance phase when treating wet AMD. Recommended and maximum dosing intervals do not differ for the three other disorders.

80 Beovu is not indicated for treatment of DME, DR, or RVO.

disclose alternative dosing schedules with longer time between injections. However, these alternatives come with precautions that the alternative intervals are not as effective as the recommended dosing interval.[81] See Attachment B-1.

(42) Although Eylea's recommended dosing for RVO calls for maintenance doses every 4 weeks, I understand that for some RVO patients, physicians will use maintenance doses with 8 week or longer intervals.[82] Because the patented dosing regimen is used for some RVO patients and may have contributed to commercial success, I include RVO treatments in the analyses presented later in my declaration.

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[81] Ex. 2189 (Eylea Label, 3/2021, at 3). ("Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.")

Ex. 2216 (Lucentis Label, 3/2018, at 4). ("Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Patients should be assessed regularly.")

[82] Ex. 2051 (Do Declaration, 2/10/2022, at ¶ 138).

7. Medicare Part B Reimbursement Policy

(43) Because angiogenic eye diseases are more likely to affect older patients (see Section 5), a large portion of anti-VEGF treatments are paid for through Medicare Part B which provides outpatient medical coverage.[83] Medicare eligibility generally begins at age 65.[84] The anti-VEGF treatments are reimbursed as Medicare Part B physician-administered drugs.[85] Physician-

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[83] Ex. 2223 (Medicare Interactive Website, Medicare Part B Covered Services, https://www.medicareinteractive.org/get-answers/medicare-covered-services/medicare-coverage-overview/summary-of-part-b-covered-services (accessed 11/22/2021)).

Ex. 2218 (Regeneron, "Eylea (aflibercept) Injection: Components of Reimbursement," c. 2015, at 3–6).

[84] Ex. 2227 (Medicare Website, When Does Medicare Coverage Start?, https://www.medicare.gov/basics/get-started-with-medicare/sign-up/when-does-medicare-coverage-start (accessed 12/15/2021)).

[85] Ex. 2223 (Medicare Interactive Website, Medicare Part B Covered Services (accessed 11/22/2021)). ("Select prescription drugs, including

administered drugs are typically purchased by physicians and then "sold" to patients upon administration.[86] This process creates two parts to Medicare Part B reimbursement – drug costs and physician fees.[87]

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immunosuppressant drugs, some anti-cancer drugs, some anti-emetic drugs, some dialysis drugs, and drugs that are typically administered by a physician.")

All anti-VEGF treatments are included in the Centers for Medicare & Medicaid Services Medicare Part B Drug Average Sales Price files.

Ex. 2172 (Centers for Medicare & Medicare Services Website, 2021 ASP Drug Pricing Files, https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files (accessed 11/22/2021)).

[86] Ex. 2165 (USC-Brookings, "Medicare Payment for Physician-Administered (Part B) Drugs: The Interim Final Rule and a Better Way Forward," 2/10/2021, at PDF 1, available at: https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2021/02/10/medicare-payment-for-physician-administered-part-b-drugs/).

[87] Ex. 2165 (USC-Brookings, "Medicare Payment for Physician-Administered (Part B) Drugs: The Interim Final Rule and a Better Way Forward," 2/10/2021, at PDF 1). ("Medicare bases payment for physician-administered medicines on

(44) Starting in 2005, physician-administered drugs were reimbursed at a drug's Average Sales Price (ASP) plus 6%.[88] "By law, a drug's ASP is defined as the volume-weighted average manufacturer sales price net of all rebates, discounts, and other price concessions to U.S. purchasers."[89] This 106% of ASP is referred to as the "payment limit."[90]

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the prices charged for products grouped together into a single billing code, plus 6 percent of the 'average sales price' (ASP) for that billing code. (Medicare also separately pays physicians for the cost of administration based its physician fee schedule rather than the cost of the medicine).")

88 Ex. 2155 (U.S. Department of Health and Human Services (ASPE), "Medicare Part B Reimbursement of Prescription Drugs," 6/2014, at 2, available at: https://aspe.hhs.gov/sites/default/files/private/pdf/106966/ib_mprpd.pdf).

89 Ex. 2155 (U.S. Department of Health and Human Services (ASPE), "Medicare Part B Reimbursement of Prescription Drugs," 6/2014, at 2).

90 Centers for Medicare & Medicaid Services Website, 2021 ASP Drug Pricing Files, https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files (accessed 11/22/2021). (" ... the payment limit determined using the current ASP+6% methodology.")

(45) In addition to drug cost reimbursement, physicians are also reimbursed for their services under the Physician Fee Schedule.[91] The fees are calculated based on a variety of factors including amount of time, technical skill, equipment, and professional liability involved in the provision of the service.[92]

Beginning in 2013, a federal sequestration order resulted in a Part B drug reimbursement falling from 106% to 104.3% of ASP.

Ex. 2268 (Weidner, Susan, et al. (2021), "Observations Regarding the Average Sales Price Reimbursement Methodology," *Evidence-Based Oncology* 27(4): 156–160, at PDF 1).

[91] Ex. 2174 (Centers for Medicare & Medicaid Services Website, Physician Fee Schedule, https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched (accessed 11/22/2021)).

Ex. 2154 (American Speech-Language-Hearing Association Website, Calculating Medicare Fee Schedule Rates, https://www.asha.org/practice/reimbursement/medicare/calculating-medicare-fee-schedule-rates/ (accessed 11/22/2021)).

[92] Ex. 2154 (American Speech-Language-Hearing Association Website, Calculating Medicare Fee Schedule Rates, (accessed 11/22/2021)).

As an example, CMS's National Coverage Policy for Eylea instructs that physicians submit two claims in order to bill for their services.[93] The first claim is a billing code with the description "Injection, aflibercept, 1mg" (despite the fact that a single injection of Eylea is a 2mg dose), and the second claim is a billing code for "Intravitreal injection of a pharmacologic agent" (i.e., the physician fee).[94]

(46) Medicare Part B does not cover the full amount of the payments owed to physicians. Instead, Medicare covers 80% of the payments, and Medicare beneficiaries (patients) are responsible for a copayment equal to the remaining

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93 Ex. 2175 (CMS.gov Medicare Coverage Database, "Billing and Coding: Aflibercept (Eylea)," 4/22/2021, at 2, available at: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=53387&ver=28&keyword=&keywordType=starts&areaId=all&docType=6,3,5,1,F,P&contractOption=all&hcpcsOption=code&hcpcsStartCode=J0178&hcpcsEndCode=J0178&sortBy=title&bc=1) .

94 Ex. 2175 (CMS.gov Medicare Coverage Database, "Billing and Coding: Aflibercept (Eylea)," 4/22/2021, at 2).

20% of the cost of both the drug and the physician's service.[95] While there are exceptions to this 80/20 split, according to Medicare.gov, macular degeneration tests and treatment require the 20% copayment.[96] That said, beneficiaries can offset the cost of copayments through participation in a

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95 Ex. 2165 (USC-Brookings, "Medicare Payment for Physician-Administered (Part B) Drugs: The Interim Final Rule and a Better Way Forward," 2/10/2021, at PDF 2). ("For the minority of patients without supplemental coverage, physicians might take into consideration the 20 percent coinsurance that patients pay.")

96 Ex. 2225 (Medicare.gov Website, Macular Degeneration Tests & Treatment, https://www.medicare.gov/coverage/macular-degeneration-tests-treatment (accessed 11/22/2021)).

Medicare Supplement policy.[97] In 2018, approximately 83% of traditional Medicare beneficiaries had some type of supplementary coverage.[98]

(47) According to CMS, most Medicare beneficiaries enrolled in Medicare Advantage plans (approximately 42% of the total Medicare population)

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[97] Ex. 2165 (USC-Brookings, "Medicare Payment for Physician-Administered (Part B) Drugs: The Interim Final Rule and a Better Way Forward," 2/10/2021, at PDF 2). (" For the minority of patients without supplemental coverage, physicians might take into consideration the 20 percent coinsurance that patients pay.")

Ex. 2154 (American Speech-Language-Hearing Association Website, Calculating Medicare Fee Schedule Rates, (accessed 11/22/2021)). ("Medicare will accept 80% of the allowable amount of the Medicare Physician Fee Schedule (MPFS) and the patient will pay a 20% co-insurance at the time services are rendered or ask you to bill their Medicare supplemental policy.")

[98] Ex. 2209 (Kaiser Family Foundation, "A Snapshot of Sources of Coverage Among Medicare Beneficiaries in 2018," 3/23/2021, at PDF 2, available at: https://www.kff.org/medicare/issue-brief/a-snapshot-of-sources-of-coverage-among-medicare-beneficiaries-in-2018/).

receive coverage for Part B drugs as part of their overall plan.[99] These plans limit exposure to out-of-pocket costs for these products.[100] Coverage for prescription drugs varies across Medicare Advantage plans and providers and across private insurance providers. Eylea is covered by most plans, including Medicare, Medicare Advantage, most commercial payers, and most state

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[99] Ex. 2226 (Medicare.gov Website, Medicare Advantage Plans, https://www.medicare.gov/sign-up-change-plans/types-of-medicare-health-plans/medicare-advantage-plans (accessed 12/31/2021)).

Ex. 2210 (Kaiser Family Foundation, "Medicare Advantage in 2021: Enrollment Update and Key Trends," 6/21/2021, https://www.kff.org/medicare/issue-brief/medicare-advantage-in-2021-enrollment-update-and-key-trends/).

[100] Ex. 2226 (Medicare.gov Website, Medicare Advantage Plans (accessed 12/31/2021)).

Medicaid plans.[101] Further, most commercial payers provide the same benefits for Eylea and Lucentis.[102]

[101] Ex. 2218 (Regeneron, "Eylea (aflibercept) Injection Components of Reimbursement," c. 2015, at 5, 6).

[102] Ex. 2218 (Regeneron, "Eylea (aflibercept) Injection Components of Reimbursement," c. 2015, at 5, 6).

8. Commercial Success

(48) Eylea has achieved commercial success as a treatment for angiogenic eye disorders. This commercial success is demonstrated by its sales since launch, by its performance relative to other available treatments, and by the nexus of these sales to the method of treatment covered by the ’338 Patent’s claims. Eylea’s historical commercial performance is discussed below.

8.1. U.S. Eylea sales and revenue

(49) Regeneron has provided gross sales and net sales of Eylea in the United States over the period from 2011 to 2021.[103] In calculating net sales, Regeneron deducts returns, rebates, and discounts from gross sales.[104] These deductions are similar to the deductions used by other pharmaceutical companies to

[103] Ex. 2285 (Regeneron, Eylea Gross & Net Sales P&L YTD, c.2021, at tab "Gross & Net Sales P&L YTD").

[104] Ex. 2285 (Regeneron, Eylea Gross & Net Sales P&L YTD, c.2021, at tab "Gross & Net Sales P&L YTD").

Ex. 2263 (Regeneron, Eylea Sales Summary, c.2020).

calculate net sales.[105] Eylea has achieved commercial success as measured by gross sales and net sales.

8.1.1. Gross sales

(50) Regeneron generated [redacted] and [redacted] in U.S. gross sales of Eylea in 2012 and 2021, respectively. See Attachment D-2. From 2012 to 2021, the compound annual growth rate was [redacted], and the absolute growth rate was [redacted]. See Attachment D-2. Cumulative U.S. gross sales of Eylea from its launch in 2011 through 2021 were [redacted].

(51) Eylea's successful growth of net and gross sales has been driven by its increasing use by physicians. In terms of unit sales, Eylea has been sold in both vials and prefilled syringes (introduced in 2019), each containing one dose (2mg) and constituting one unit. See Attachment D-1. In 2012, Regeneron sold [redacted] units of Eylea in the U.S., and in 2021, Regeneron sold [redacted] units in the U.S. See Attachment D-2. This demonstrates a

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[105] See for example:

Ex. 2256 (Roche, "Finance Report", 2020, at 63).

Ex. 2230 (Novartis, "Annual Report", 2020, at 65).

Ex. 2160 (Bausch Health Companies, Form 10-K, 2020, at 77).

compound annual growth rate of [redacted], and an absolute growth rate of [redacted] over the period.[106] See Attachment D-2. Cumulative U.S. unit sales of Eylea from its launch in 2011 through 2021 were [redacted] units.[107]

8.1.2. Net sales

(52) In 2012, the first full calendar year following Eylea's launch, Regeneron generated $837.94 million in total net sales. See Attachment D-2. Since 2012, Eylea has realized positive year over year growth in net sales in every year, with all but one year (2020) experiencing double digit percentage sales growth. See Attachment D-2. In 2021, Eylea achieved $5.8 billion in U.S. net sales. See Attachment D-2. Consistent with this level of success domestically, one online source reported that Eylea ranked 6th in global drug sales.[108]

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[106] Differences in calculated growth rates for unit sales and gross sales are due to rounding of gross sales values. See Attachment D-2.

[107] Since Regeneron launched its Eylea PFS version in 2019, nearly all unit sales have converted to PFS. See Attachment D-1.

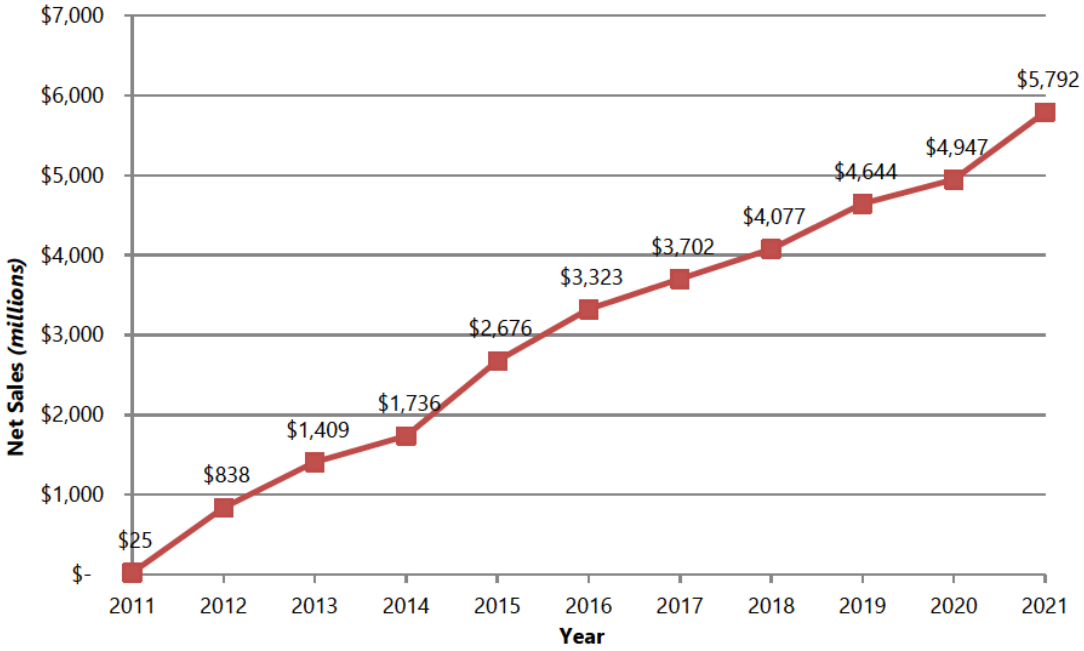
[108] Ex. 2194 (FiercePharma, "The Top 20 Drugs by Worldwide sales in 2020," 5/3/2021, https://www.fiercepharma.com/special-report/top-20-drugs-by-2020-sales).

Despite the fact that Regeneron has not increased the price of Eylea since its launch in 2011,[109] Eylea's U.S. net sales grew at a compound annual rate of 24.0% and an absolute rate of 591.3% from 2012 to 2021. See Attachment D-2. Total cumulative U.S. net sales of Eylea from its launch in 2011 through 2021 were $33.2 billion. Chart 1 below illustrates the growth in U.S. net sales of Eylea. See Attachment D-7.

[109] See Attachment D-6.

Ex. 2229 (Regeneron, WAC Pricing File, 5/2021, at tab "Analysis").

Chart 1: Eylea U.S. Net Sales (2011–2021)



8.2. U.S. Eylea profits

(53) Regeneron has earned substantial profit from its sales of Eylea. Regeneron evaluates Eylea's financial performance by calculating gross profits and operating profits, common performance metrics for companies in the biopharmaceutical industry.[110] Eylea's gross profits are calculated by subtracting costs of goods sold (COGS) such as product manufacturing costs (referred to in the commercial P&L for Eylea as "Drug"), royalties (including

[110] Conversation with Regeneron Executive Director, Commercial Finance & Business Planning and Senior Director, FP&A.

royalties to Genentech and [redacted]), and spoilage costs from net product sales.[111] Table 4 below illustrates the P&L line items for Eylea. See Attachment D-1.

[111] Ex. 2200 (Regeneron, "U.S. Eylea Historical Brand P&L," 5/2021, at 2).

A complete P&L for Eylea can be found in Attachment D-1.

Table 4: U.S. Eylea P&L Example *(values in millions)*

Metric	2020	2021
Gross sales [a]	[redacted]	[redacted]
Gross sales deductions [b][112]	[redacted]	[redacted]
Net sales [c = a + b]	$4,947.2	$5,792.3
Total cost of goods sold [d]	[redacted]	[redacted]
Drug	[redacted]	[redacted]
Royalty	[redacted]	[redacted]
Spoilage & reserves	[redacted]	[redacted]
Total other operating costs [e]	[redacted]	[redacted]
External expenses	[redacted]	[redacted]
People expenses	[redacted]	[redacted]
Pharma fee	[redacted]	[redacted]
Gross profit [f = c - d]	[redacted]	[redacted]
Operating profit [g = c - e]	[redacted]	[redacted]

[112] Gross sales deductions refer to line items deducted from gross sales to obtain net sales. Deductions for Eylea include reserves, Medicare rebates, co-pay

(54) Gross profits from Eylea sales in the U.S. have grown from [redacted] in 2011, or [redacted] of 2011 net sales, to [redacted] in 2021, or [redacted] of 2021 net sales. See Attachment D-1. From 2011 through 2021, Regeneron earned [redacted] in gross profits from sales of Eylea in the U.S., or [redacted] of total net sales over the same period. See Attachment D-1.

(55) Regeneron calculates operating profits by subtracting additional expenses, including marketing expenditures (referred to as "External Expenses"), labor costs (referred to as "People Expenses"), and the branded prescription drug fee under the Affordable Care Act (referred to as "Pharma Fee") from gross profits.[113] Operating profits from sales of Eylea in the U.S. have grown from [redacted] in 2011, or [redacted] of 2011 net sales, to [redacted] in 2021, or [redacted] of net sales. See Attachment D-1. From 2011 through 2021, Regeneron earned

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assistance, chargebacks, rebates, discounts, and specialty pharmacy, distributor, and credit card fees. See Attachment D-1.

113 Ex. 2200 (Regeneron, "U.S. Eylea Historical Brand P&L," 5/2021, at 3).

Conversation with Regeneron Executive Director, Commercial Finance & Business Planning and Senior Director, FP&A.

[redacted] in operating profits from sales of Eylea in the U.S, or [redacted] of total net sales over the same period. See Attachment D-1.

8.3. Eylea's share of anti-VEGF sales

(56) In addition to sales since launch, a product's performance relative to other available products provides evidence of commercial performance that may demonstrate commercial success. The performance of other products provides context necessary for evaluating whether a patented product was commercially successful. Moreover, if a patented product captures sales previously made by other products, the patented product demonstrates that it offers, at least for some consumers, a value proposition superior to that offered by the previously available products. After establishing a nexus to the patented features, these captured sales can demonstrate demand for the patented features and that the patented feature directly contributed to the commercial success of the product

(57) Because of the price disparities of the treatments being compared in this matter (see Section 8.4), relative performance is evaluated using "share of sales" measures, either share of unit sales or share of treated patients. Such measures isolate treatment uptake from price disparities. For simplicity, I refer to both measures as "sales shares" or "share of sales."

8.3.1. Data sources

(58) For analysis of relative sales performance among potential treatments for the relevant angiogenic eye disorders, I rely on three data sources: Medicare Part B physician treatment data provided by the Centers for Medicare & Medicaid Services (CMS), Vestrum data, and Regeneron's Awareness, Trial, and Usage (ATU) surveys. Each of these data sources is described below. I consider all three data sources as each has its respective merits. However, all of the data sources show strong sales growth and overall sales share for Eylea since launch.

Medicare Part B services and procedures

(59) CMS reports annual usage of physician services paid under Medicare Part B over the period from 2012 to 2019 (the latest year available).[114] Medicare Part

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[114] Data first became available in 2012. See:

Ex. 2220 (Manning, Richard, et al. (2015), "Similar Products at Different Prices: Can Biopharmaceutical Companies Segment Markets?" *International Journal of the Economics of Business* 22(2): 231–243, at 234). ("Recently, the Centers for Medicare and Medicaid Services made available to the public for

B data provide information on services and procedures provided to Medicare Part B beneficiaries by physicians and other healthcare professionals, aggregated by provider and service.[115] The data contain information including

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the first time detailed data regarding the Medicare Part B program. The data cover all of 2012…")

The latest available data is 2019. See: Ex. 2168 (Centers for Medicare & Medicaid Services Website, Medicare Physician & Other Practitioners - by Provider and Service, (accessed 11/19/2021)).

Medicare has four components. Part A provides coverage for inpatient/hospital care; Part B provides coverage for physician care, Part C (also referred to as Medicare Advantage) provides Parts A and B services via a private health plan; and Part D provides prescription drug coverage. See:

Ex. 2224 (Medicare Interactive Website, The Parts of Medicare (A, B, C, D), https://www.medicareinteractive.org/get-answers/medicare-basics/medicare-coverage-overview/original-medicare (accessed 11/30/2021)).

[115] Ex. 2168 (Centers for Medicare & Medicaid Services Website, Medicare Physician & Other Practitioners - by Provider and Service, (accessed 11/19/2021)).

services provided, drugs administered, and the amounts paid by Medicare Part B for those services and drugs.[116] For example, for all relevant conditions, the file for 2019 contains more than 10.1 million records of data for more than 1 million healthcare providers.[117] The Medicare Part B data have various attributes that affect the analysis and provide insight into the share of relevant sales captured by Eylea.

- As indicated, Medicare Part B data are not limited to treatments for angiogenic eye disorders, but contain all services and procedures paid for under Medicare Part B. Because treatments like Avastin are used in settings other than angiogenic eye disorders (i.e., in treating cancer), calculating total treatments (and from these, shares of sales) using each relevant drug or biologic would not reflect the portion of people with relevant angiogenic eye disorders who received these treatments. In order

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116 Ex. 2220 (Manning (2015), at 234).

117 See 2019 data file at:

Ex. 2168 (Centers for Medicare & Medicaid Services Website, Medicare Physician & Other Practitioners - by Provider and Service, (accessed 11/19/2021)).

to analyze sales shares of anti-VEGF treatments for the relevant indications paid for by Medicare Part B, I restrict the sample to include payments for treatments administered only by ophthalmologists.[118]

- The Medicare Part B dataset lacks information about underlying patient conditions being treated, so shares of sales by product can only be calculated in aggregate across all indications (rather than separately for, e.g., wet AMD and DR) treated by ophthalmologists.
- As indicated above, these data are reported annually and are available for the years 2012 through 2019. See Attachment X-3. Notably, these data include three of the four anti-VEGF treatment options (Eylea, Lucentis, and Avastin) and several of the other treatment options (e.g., Visudyne, and Macugen). See Attachment X-3. As discussed below, the other available data sources used in the sales share analysis focus on the anti-VEGF treatment options of Eylea, Avastin, Lucentis, and Beovu.

Vestrum Health

(60) Vestrum Health is a company that gathers and analyzes data from electronic health records and packages them for sale to retina practices and

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[118] This is consistent with the analytical approach used in: Ex. 2220 (Manning (2015), at 235). ("Specifically, we limited the data to ophthalmologists…")

pharmaceutical companies, including Regeneron.[119] Regeneron uses data from Vestrum in the course of its business to assess the commercial performance of its products.[120] Specifically, Regeneron began using Vestrum data in 2019 to supplement its use of ATU survey responses in comparing sales of Eylea, Avastin, Lucentis, and Beovu.[121] The Vestrum data provided cover a period beginning in 2016.

- The Vestrum data are presented in quarterly reports on the sales shares of the four most commonly used anti-VEGF treatment options (i.e., Eylea, Lucentis, Avastin, and Beovu). See Attachment X-1. Vestrum data are available from 2016-Q1 to 2021-Q4. In addition, the Vestrum data include indication-level sales shares. In other words, the sales shares of Eylea,

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[119] Ex. 2265 (Vestrum Health Website, Homepage, https://www.vestrumhealth.com/index.php (accessed 1/3/2022)).

Ex. 2266 (Vestrum Health Website, Pharmaceutical Companies, https://www.vestrumhealth.com/pharma.php (accessed 1/3/2022)).

[120] Conversation with Regeneron Director, Customer Insights.

For example: Ex. 2272 (Regeneron, "Eylea Q2 2021 Performance," 8/2/2021).

[121] Conversation with Regeneron Director, Customer Insights.

Lucentis, Avastin, and Beovu are calculated separately for patients with wet AMD, with DR, with DME, and with RVO. See Attachment X-1.

Regeneron ATU surveys

(61) The third source of data on sales shares is Regeneron's ATU surveys. These are quarterly surveys of approximately 200 eye care practitioners in the U.S., or approximately 6% of the over 3,000 ophthalmologists and retinal specialists that treat the relevant diseases.[122] See Section 5. Samples of this size are consistent with common practice in market research.[123] Moreover, the

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[122] Ex. 2176 (Regeneron, "Q4 2020 Performance Update Wet AMD, DME, MEfRVO & DR w/out DME," 1/29/2021, at 136).

Conversation with Regeneron Director, Customer Insights.

[123] Ex. 2195 (FocusVision, "Survey Sample Size: How Much Do I Need?" 4/11/2019, https://www.focusvision.com/blog/survey-sample-size-how-much-do-i-need/).

Under standard calculation approaches, sample sizes of 200 for a population of 3,000 physicians yields a 6.7% margin of error.

Ex. 2171 (CloudResearch Website, Determining Sample Size: How Many Survey Participants Do You Need?

presentations summarizing survey responses regularly contain results from statistical testing for differences between anti-VEGF treatments.[124]

- Regeneron's "Eylea brand team" began the ATU survey in 2011 to assess "the current state of the market on several critical metrics (awareness, opinions[,] and behavior)."[125] Regeneron has published the results and key takeaways in quarterly, internal reports. The surveys provide information

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https://www.cloudresearch.com/resources/guides/statistical-significance/determine-sample-size/ (accessed 1/25/2022)).

Ex. 2166 (Calculator.net Website, Sample Size Calculator, https://www.calculator.net/sample-size-calculator.html?type=2&cl2=95&ss2=200&pc2=50&ps2=3000&x=68&y=18#findci (accessed 1/25/2022)).

[124] For example: Ex. 2176 (Regeneron, "Q4 2020 Performance Update Wet AMD, DME, MEfRVO & DR w/out DME," 1/29/2021, at 11-18).

[125] Ex. 2197 (Regeneron, "Physician ATU – Benchmark Wave," 9/15/2011, at 2).

on relative product performance, drivers of physician treatment choice, and physician dosing practices, among other information.[126]

- One of the key topics covered in the ATU surveys is the shares of the four most commonly used anti-VEGF treatment options (i.e., Eylea, Lucentis, Avastin, and Beovu). See Attachment X-2. Additionally, indication level data are available. See Attachment X-2.

(62) As discussed above, data from these three sources are used to calculate unit share (Vestrum) or patient share measures (Medicare Part B; ATU surveys). Patient shares for the Medicare Part B data are calculated by aggregating the number of unique Medicare beneficiaries that received each treatment. See Attachment X-3. Patient shares for the ATU data are reported within the produced documents as the share of treated eyes. For Vestrum data, generally Regeneron's presentations refer to the projections as a measure of the share of injections.[127]

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[126] For example: Ex. 2176 (Regeneron, "Q4 2020 Performance Update Wet AMD, DME, MEfRVO & DR w/out DME," 1/29/2021).

Conversation with Regeneron Director, Customer Insights.

[127] Ex. 2272 (Regeneron, "Eylea Q2 2021 Performance," 8/2/2021).

(63) In my analyses of Eylea's share of sales, I consider all three data sources. When discussing Eylea's share of sales, I do not distinguish between Eylea's share including non-anti-VEGF treatments (Medicare Part B) and its share excluding them (Vestrum and ATU). This is a reasonable simplification as the anti-VEGF treatments account for the vast majority of treatments (e.g., 95.4% as of 2019). See Attachment C-1. Further, this simplification does not impact any important conclusions of the analysis.

8.3.2. Eylea's historic patient share as an indicator of commercial success

(64) Eylea was approved for sale in the U.S. by the FDA on November 18, 2011 for the treatment of wet AMD.[128] The product was quickly adopted by physicians, and according to ATU data by the first quarter of 2012, it achieved

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Although one presentation described Vestrum as measuring treated eyes, the August 2021 presentation characterized it as measuring injection shares.

Ex. 2275 (Regeneron, "Vestrum Anti-VEGF Market Share Adjustment Overview," 5/10/2019, at 3).

[128] Ex. 2181 (Drugs.com Website, Eylea FDA Approval History, https://www.drugs.com/history/eylea.html (accessed 11/16/2021)).

Ex. 2185 (Eylea Label, 11/2011, at 1).

an [redacted] sales share among patients with wet AMD who were treated using the major anti-VEGF treatments (Eylea, Avastin, or Lucentis). See Attachment X-2. By the end of 2012, Eylea's sales share was between [redacted] and [redacted] (depending on the data source used). See Attachment C-1. By the end of 2021, Eylea's overall sales share (across all relevant indications) was between [redacted] and [redacted], making it the largest selling product in the product category. See Attachment C-1. Chart 2 illustrates the rapid rise in Eylea's patient share since its launch. See Attachment C-6. As discussed in greater detail below, Eylea achieved a sales share similar to Avastin's despite the latter's substantially lower price. See Section 8.4.

Chart 2: Eylea's Sales Share Across Different Data Sources – All Indications[129]

(65) This trend of success holds true across each indication for which Eylea is approved. In general, when Eylea has been approved for a new indication, it

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[129] In this chart and all other charts related to sales shares, data for 2021 reflect the most current data produced by Regeneron. For ATU, data through 2021-Q2 has been produced. For Vestrum, data through 2021-Q4 has been produced. See Attachment X-1 and X-2.

Medicare Part B: A linear regression of Eylea Patient Share on Year results in a slope of ~3.8%*** (p-value of ~0.0006).

has quickly gained sales, achieving a share of sales of about [redacted] or more in the first year and rising to achieve the highest or second highest share of sales in the relevant category by 2021.[130] See Attachments C-2, C-3, C-4, and C-5.

(66) As shown in Chart 3, for wet AMD, Eylea achieved a sales share of [redacted] in 2012, its first full year following launch. Its share has gradually increased each year and by the end of 2021, Eylea's share was 44.0% in the ATU survey and [redacted] in the Vestrum data. According to ATU and Vestrum data, Eylea is currently the most widely used product for wet AMD, with off-label Avastin being second with an ATU sales share of 39.0% and a Vestrum sales share of [redacted]. See Attachment C-2.

ATU: A linear regression of Eylea Patient Share on Year results in a slope of ~3.3%*** (p-value of ~0.0005).

Vestrum: A linear regression of Eylea Patient Share on Year results in a slope of ~1.5% (p-value of ~0.14).

[130] For DR without DME, the Vestrum data shows Avastin with a large sales share and Eylea capturing an [redacted] sales share in its first year. These numbers are incongruent with the ATU survey as well as Vestrum's total sales share statistics in Attachment C-1. See Attachment C-4.

Chart 3: Eylea's Sales Share Across Data Sources – Wet AMD[131]

(67) Eylea was approved to treat DME in July 2014.[132] As shown in Chart 4, for DME, Eylea achieved a sales share of [redacted] in 2014. The sales share increased sharply again in 2015 to [redacted]. By the end of 2021, Eylea's sales

131 ATU: A linear regression of Eylea Patient Share on Year results in a slope of ~3.3%*** (p-value of ~0.0004).

Vestrum: A linear regression of Eylea Patient Share on Year results in a slope of ~2.1%** (p-value of ~0.02).

132 Ex. 2247 (Regeneron Press Release, "Eylea Injection Receives FDA Approval for the Treatment of Diabetic Macular Edema (DME)," 7/29/2014).

share in the DME indication was somewhere between 44.0% (ATU) and [redacted] (Vestrum). According to both Vestrum and ATU data, Eylea has the highest share among all anti-VEGF products for the treatment of DME. See Attachment C-3.

Chart 4: Eylea's Sales Share Across Data Sources – DME[133]

(68) Measures of sales share for patients with DR without DME vary more greatly across data sources than measures for other indications.[134] However, both

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[133] ATU: A linear regression of Eylea Patient Share on Year results in a slope of ~4.5%*** (p-value of ~0.01).

Vestrum: A linear regression of Eylea Patient Share on Year results in a slope of ~1.3% (p-value of ~0.11).

[134] The differences in sales share for DR patients likely is due to the different data sources and methodologies used by Regeneron to calculate those measures. For

ATU and Vestrum data show an upward trend in sales share for Eylea since obtaining FDA approval in 2019 for treating DR without DME.[135] As shown in Chart 5, Eylea's sales share for DR without DME patients has grown since it was first tracked.[136] According to ATU data, Eylea achieved a sales share of 29.0% in 2017, which rose to 37.0% by the end of 2021, an increase of 8.0

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example, one possible explanation for the difference between the Vestrum and ATU data is that the Vestrum data may capture use of Avastin in conjunction with laser treatments, whereas the ATU data does not. Regardless, the different measures both demonstrate growth in sales share for Eylea.

Conversations with Director, Customer Insights.

[135] The FDA approved Eylea to treat DR without DME on May 13th, 2019. See Section 6.2.4.

[136] The FDA approved Eylea to treat DR without DME on May 13th, 2019. See Section 6.2.4.

Moreover, Eylea sales to treat DR without DME represent approximately 1.1% of its total sales.

Ex. 2276 (Regeneron, "Eylea Q2 2020 Performance (Vestrum Projection Data)," 8/4/2020, at 27).

percentage points. See Attachment C-4. At the end of 2021, Eylea was the second largest anti-VEGF therapy behind Avastin in DR without DME, which had a sales share of 40.0%. The Vestrum data shows a similar increase in utilization, with Eylea's sales share increasing [redacted] percentage points from [redacted] in 2016 to [redacted] in 2021. According to Vestrum, by the end of 2021, Eylea was second to Avastin, which had a sales share of [redacted]. See Attachment C-4.[137]

[137] Sales for DR without DME have been limited, with Eylea 2020 sales for DR without DME accounting for 1.1% of total Eylea sales.

Ex. 2276 (Regeneron, "Eylea Q2 2020 Performance (Vestrum Projection Data)," 8/4/2020, at 27).

Chart 5: Eylea's Sales Share Across Data Sources – DR without DME[138]

(69) As shown in Chart 6, for RVO, Eylea achieved a sales share of [redacted] in 2013, its first full year with an indication for RVO.[139] Starting in 2014, the ATU survey began tracking Eylea's sales share for CRVO and BRVO patients separately. In both cases, Eylea achieved a sales share of approximately 40%

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[138] ATU: A linear regression of Eylea Patient Share on Year results in a slope of ~3.4% (p-value of ~0.17).

Vestrum: A linear regression of Eylea Patient Share on Year results in a slope of ~2.9%** (p-value of ~0.02).

[139] Eylea was indicated for RVO in September 2012. See Attachment B-1.

in 2015, which has grown slowly through 2021. Eylea's sales share by the end of 2021 was somewhere between 46.0% (ATU, CRVO) and [redacted] (Vestrum, All RVO). According to ATU and Vestrum data, Eylea currently has the highest sales share among anti-VEGF products used for RVO patients with Avastin in second. See Attachment C-5.

Chart 6: Eylea's Sales Share Across Data Sources – RVO[140]

8.3.3. Eylea's displacement of other anti-VEGF treatments as an indicator of commercial success

(70) Eylea's increased utilization has come at the expense of two available and established anti-VEGF treatments, Avastin and Lucentis, which had been in wide use for several years before Eylea's introduction.

[140] ATU CRVO: A linear regression of Eylea Patient Share on Year results in a slope of ~2.5%** (p-value of ~0.02).

(71) Economics recognizes a first mover advantage, which is that established products have an advantage that later entrants must overcome. This advantage arises because the familiarity that consumers (and physicians in this case) have with incumbent products leads to a certain degree of inertia in consumer demand or product utilization.[141] In order to displace incumbent products, purchasers must be persuaded that a later entrant has benefits to them that are not provided by an incumbent product. Those benefits can include a lower price, beneficial features, or other attributes that consumers find attractive.

ATU BRVO: A linear regression of Eylea Patient Share on Year results in a slope of ~1.5% (p-value of ~0.18).

Vestrum RVO: A linear regression of Eylea Patient Share on Year results in a slope of ~3.1%*** (p-value of ~0.002).

[141] Ex. 2211 (Ling, Davina C., et al. (2002), "Deregulating Direct-To-Consumer Marketing of Prescription Drugs: Effects on Prescription and Over-The-Counter Product Sales," *Journal of Law and Economics*, XLV:691–723, at 698).

New entrants must typically spend resources in marketing to overcome the advantages of incumbency enjoyed by pre-existing products.[142]

(72) According to ATU data, prior to Eylea's launch, Avastin and Lucentis accounted for 63.0% and 37.0% of anti-VEGF sales. See Attachment C-1. Similarly, Medicare Part B data for 2012 (the first year available) show that Avastin and Lucentis were used on 39.4% and 35.5% of patients given ophthalmic treatment options. See Attachment C-1.

(73) Although Eylea's growth has coincided with overall anti-VEGF sales growth, evidence demonstrates that at least a portion of Eylea's growth has come from patients that otherwise would have received Avastin or Lucentis. For example, Medicare Part B data shows that Eylea was used for an increasing number of patients each year from 2012 through 2019, whereas Avastin (2015, 2019) and Lucentis (2014–2017) both have seen multiple years with declining

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[142] Ex. 2211 Ling (2002). ("In the current context, it is worth emphasizing that Zantac was able to overcome Tagamet's first-mover advantage in the Rx market in part by employing aggressive marketing efforts that conveyed information on Zantac's claimed advantages—more convenient daily dosing, fewer side effects, and fewer adverse interactions with other drugs than Tagamet.")

patients during that period, showing that Eylea's growth came at least in part from patients that otherwise would have used one of those two products in those years.[143] See Attachment E-2. Further, Eylea's patient share for second line of therapy is [redacted] and [redacted] for wet AMD, DME, and DR, respectively.[144]

(74) The sales shares of both Avastin and Lucentis peaked around 2011 and have since declined steadily. See Attachment C-1. Chart 7 below illustrates Avastin's and Lucentis's sales share passing to Eylea since Eylea's launch in late 2011. Since Eylea's launch, the decline in sales shares for Avastin and Lucentis has been approximately equal, with Avastin losing 23.9 percentage points and Lucentis losing 21.6 percentage points. See Attachment C-11.

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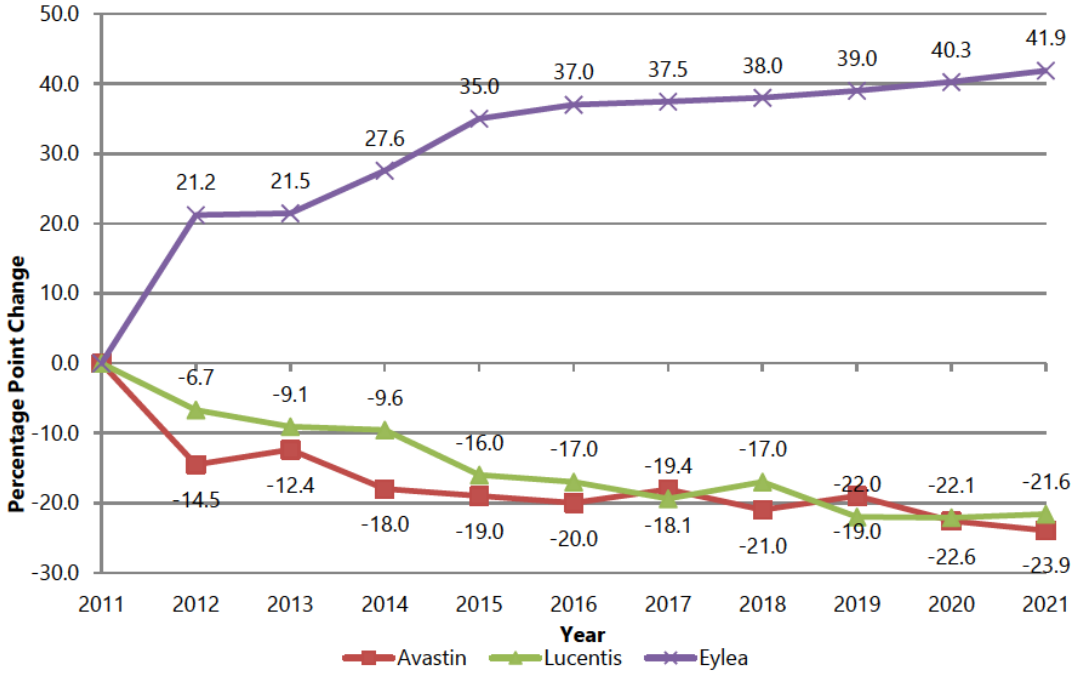
[143] Moreover, even in years during which all three anti-VEGF treatments were used on more patients, had Eylea not been available it is likely that Avastin and Lucentis would have been used for at least some of the patients who historically were treated with Eylea.

[144] Ex. 2278 (Regeneron, "Wave 1 2021 Performance Update Wet AMD, DME, MEfRVO, and DR w/out DME," 9/2021, at 78, 81, 90).

Chart 7: Percentage Point Change in Sales Share Since Eylea Launch – All Indications, ATU Data[145]



(75) Medicare Part B data show a similar trend with Lucentis losing 14.0 percentage points since 2012 and Avastin losing 8.8 percentage points. See

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145 Avastin: A linear regression of Percentage Point Change on Year results in a slope of ~-1.6p.p.*** (p-value of ~0.002).

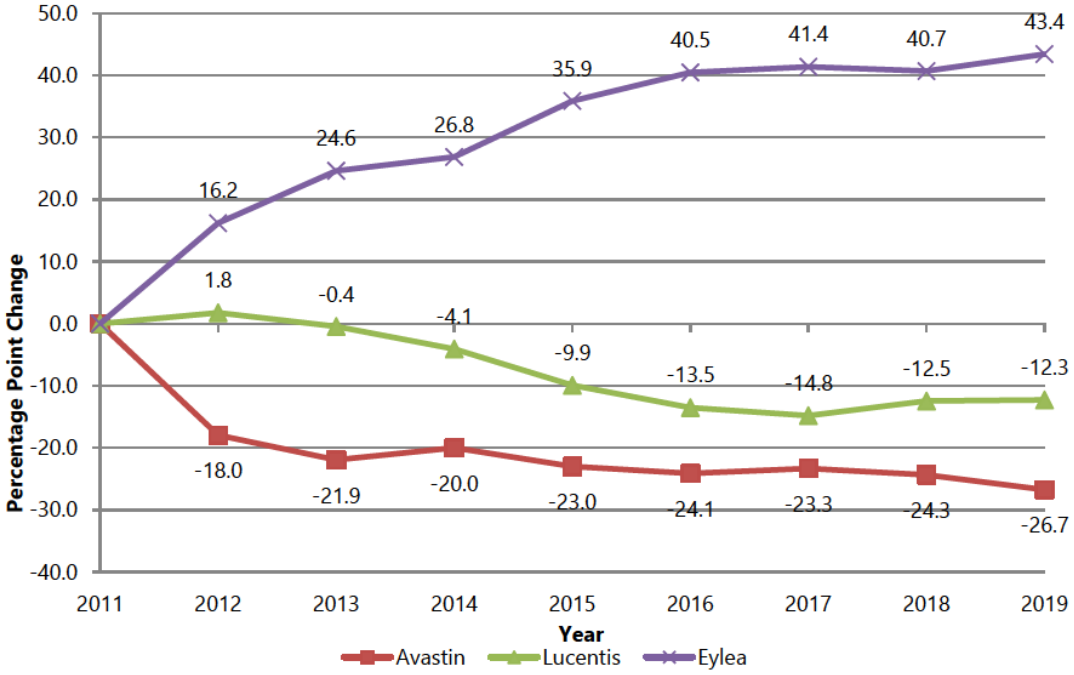
Lucentis: A linear regression of Percentage Point Change on Year results in a slope of ~-2.1p.p.*** (p-value of ~0.00002).

Eylea: A linear regression of Percentage Point Change on Year results in a slope of ~3.3p.p.*** (p-value of ~0.0005).

Attachment C-1. Chart 8 below shows the cumulative percentage point change in sales shares since Eylea launched. See Attachment C-12.[146]

[146] Charts 7 and 8 focus on Eylea's displacement of Avastin and Lucentis. The limited data available also indicate that Eylea has displaced Beovu's sales share as Beovu's share fell as safety concerns for the product emerged. As discussed in Section 6.2.5, according to Vestrum data Beovu's sales share peaked in 2020-Q1 and declined quickly thereafter. From 2020-Q1 to 2020-Q2 Beovu's sales share in wet AMD declined by 2.6 pp. See Attachment X-1. Meanwhile, Eylea's sales share in wet AMD grew 2.8 pp. See Attachment X-1. Further, from 2020-Q1 to 2021-Q2 Eylea's sales share in wet AMD grew 4.6 pp while Beovu's declined 3.0 pp. See Attachment X-1. During this same time period, Avastin's wet AMD sales share was stagnant, and Lucentis' wet AMD sales share declined, indicating that Beovu's lost wet AMD sales share has been gained by Eylea.

Chart 8: Percentage Point Change in Sales Share Since Eylea Launch – All Indications, Medicare Part B Data[147]



8.3.4. Eylea status as physicians' most used treatment

(76) In addition to the analysis of sales shares, the therapy choices of individual practitioners further illustrate Eylea's commercial success as it has displaced

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147 Since Medicare Part B data begin in 2012, not 2011, the shares of Avastin and Lucentis are estimated. I use the 2011 ATU data share and adjust the numbers downward for each treatment in order to account for the fact that Medicare Part B data includes several minor treatment options (e.g., Visudyne).

Avastin and Lucentis in therapeutic use. Physicians do not necessarily prescribe one treatment to all their patients. Instead, practitioners utilize a variety of the treatment options depending upon the circumstances of the patient.[148] That said, Medicare Part B prescription data show that practitioners tend to use one treatment more often than others. In 2012, Avastin and Lucentis were the two most common treatment options, with Avastin being used most commonly by 46.4% of practitioners and Lucentis by 33.4% of practitioners. See Attachment E-1. Since 2012, Eylea has become the most commonly used treatment option for a larger share of practitioners than any

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Avastin: A linear regression of Percentage Point Change on Year results in a slope of ~-2.2p.p.** (p-value of ~0.02).

Lucentis: A linear regression of Percentage Point Change on Year results in a slope of ~-2.2p.p.*** (p-value of ~0.0009).

Eylea: A linear regression of Percentage Point Change on Year results in a slope of ~4.9p.p.*** (p-value of ~0.0004).

148 Ex. 2220 (Manning (2015), at 241). ("Rather, it is consistent with the notion that physicians typically exercise medical judgment or are responsive to other factors on a patient-by-patient basis.")

other treatment option, with 45.0% of practitioners using Eylea more than the other treatment options. Meanwhile, the percent of practitioners using Avastin and Lucentis as their most common treatment has fallen significantly, particularly for Lucentis. See Attachment E-1. Table 5 below illustrates that Eylea has become the most common treatment for practitioners and has gained share while all other available products, Lucentis and Avastin in particular, have lost share. See Attachment E-1.

Table 5: Anti-VEGF Ophthalmic Treatment Options
Medicare Part B Prescription Data[149]

Treatment	2012	2019	Gain/Loss (Percentage Points)
Eylea	12.18%	44.97%	+32.79 pp
Avastin	46.35%	38.82%	-7.53% pp
Lucentis	33.43%	11.96%	-21.47% pp

[149] Table 5 presents only anti-VEGF treatment options. A more complete presentation of treatment options (including Macugen, corticosteroids, etc.) is presented in Attachment E-1.

8.4. Price has not hindered Eylea's commercial success

(77) Economic theory clearly dictates that a product's price affects its quantity demanded. Hence, Eylea's price should be considered in an analysis of commercial success. All else the same, a product with a lower price should have greater consumer utilization than do products with higher prices. The available data show that price disparities between Eylea and other treatment options have not hindered its commercial success, so clearly, in this situation, "all else is not the same." The extended dosing interval of Eylea has allowed it to succeed in the face of other products with lower prices.

(78) Generally, among available anti-VEGF products, list prices have remained stable over time:

- Eylea's list price of $1,850 has not changed since Eylea's launch.[150]
- Lucentis's list prices, which also have stayed constant since Lucentis's launch, depend upon the dosage. The 0.5mg dose of Lucentis, used for treating wet AMD and RVO, has had a list price of $1,950, while the 0.3mg dose, used for treating DME and DR, has had a list price of $1,170.[151]

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150 Ex. 2229 (Regeneron, WAC Pricing File, 5/2021, at tab "Analysis").

151 Ex. 2229 (Regeneron, WAC Pricing File, 5/2021, at tab "Analysis").

- Avastin's list price per injection for the treatment of angiogenic eye disorders (i.e., per 1.25 mg dose) has changed over time, but was $9.96 as of May 2021.[152]
- Beovu's list price is $1,850 and has not changed since launch.[153]

(79) List price histories indicate that Eylea's price disparity with Avastin has not hindered its commercial success, and that Eylea's list price has been comparable to those of other FDA-approved anti-VEGF treatments. However, list prices do not fully reflect the prices experienced by physicians, patients, and payors.

(80) To further compare prices across the treatments, I use payment limits for Medicare Part B prescription drug reimbursement. As explained in Section 7,

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Lucentis' price varies based on condition because the recommended dosage for Lucentis differs across conditions. See Attachment D-6. For wet AMD and RVO, the recommended dose of Lucentis is 0.5 mg (0.05 mL), whereas for DME and DR the recommended dose of Lucentis is 0.3mg (0.05 mL). See Attachment B-1.

[152] Ex. 2229 (Regeneron, WAC Pricing File, 5/2021, at tab "Analysis").

[153] Ex. 2229 (Regeneron, WAC Pricing File, 5/2021, at tab "Analysis").

Medicare reimbursement for Medicare Part B drugs is set at 106% of the drug's ASP and is referred to as the payment limit.[154] The payment limit is an appropriate measure to evaluate because it reflects manufacturer rebates and discounts, and it incorporates the reimbursement for physician administration. See Section 7. CMS has published the payment limits for Part B covered drugs on its website annually since 2005.[155]

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[154] Actual reimbursements are closer to 104.3% of ASP due to a federal sequestration order; however, CMS publishes the payments limit data using a 6% mark up. See Section 7.

[155] Ex. 2173 (Centers for Medicare & Medicare Services Website, Medicare Part B Drug Average Sales Price, https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice (accessed 12/8/2021)).

Ex. 2172 (Centers for Medicare & Medicare Services Website, 2021 ASP Drug Pricing Files (accessed 11/22/2021)). ("The files below contain the payment amounts that will be used to pay for Part B covered drugs for the fourth quarter of 2021. The October 2021 ASP payment limits have been updated … Where applicable, the payment amounts in the quarterly ASP files are 106 percent of

(81) In my analysis, Medicare Part B payment limit data from 2012 to 2021 were aggregated into a single dataset. See Attachment X-6. This dataset was used to obtain annual payment limits per HCPCS code (and HCPCS code dosage amount) for various therapies used to treat the relevant angiogenic eye disorders.[156] See Attachment D-5.

(82) However, the HCPCS code dosages for the various therapies do not necessarily reflect the volume used in a single treatment using those therapies. For example, Eylea's HCPCS code dosage is 1mg, but the recommended dose

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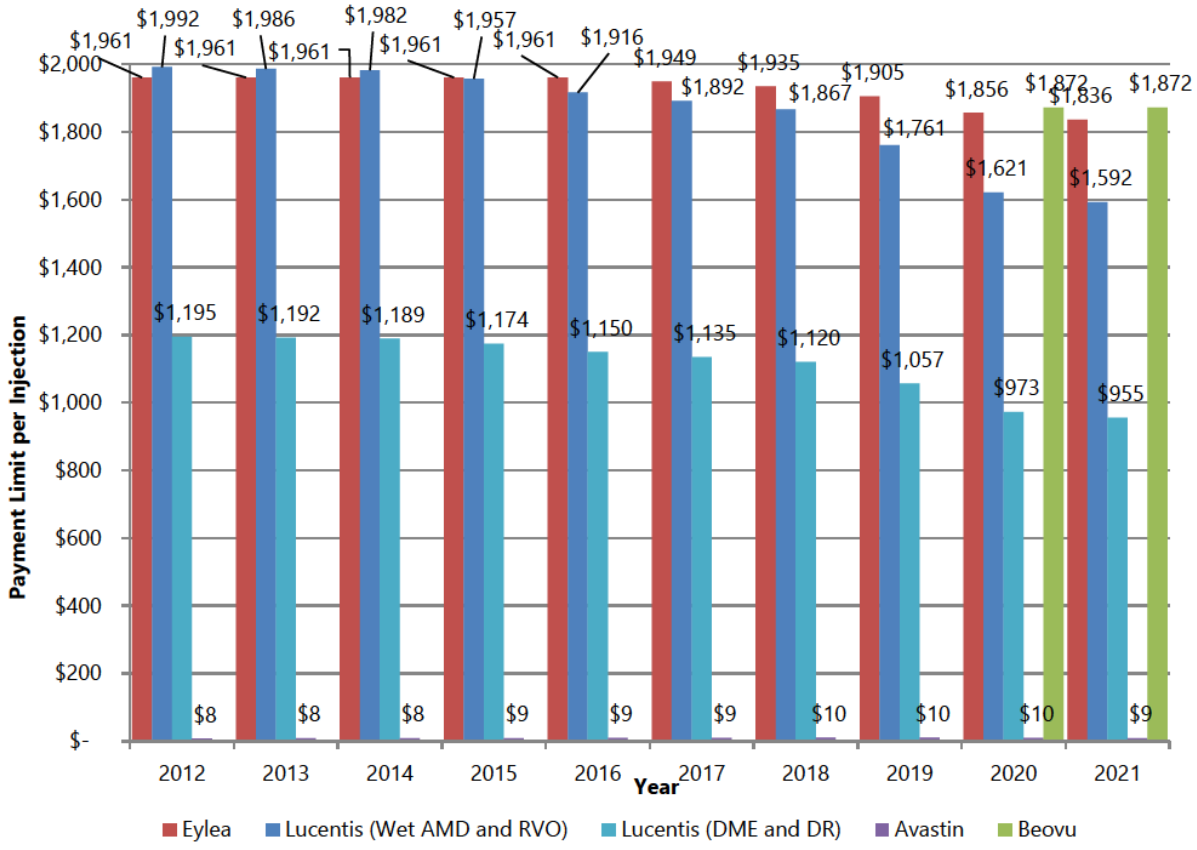
the Average Sales Price (ASP) calculated from data submitted by drug manufacturers. The quarter to quarter price changes are generally the result of updated data from the manufacturers of these drugs.")

[156] HCPCS stands for Healthcare Common Procedure Coding System. HCPCS codes are used for billing Medicare & Medicaid patients. The HCPCS codes represent procedures, supplies, products, and services which may be provided to Medicare beneficiaries and to individuals enrolled in private health insurance programs. See:

Ex. 2202 (HCPCS Codes Website, HCPCS Codes, https://hcpcs.codes/ (accessed 1/6/2022)).

per injection is 2mg. See Attachments B-1 and D-6. Therefore, to calculate the payment limit per injection for anti-VEGF products, the annual payment limits reported in CMS data are multiplied by a conversion factor to calculate annual payment limits per treatment for the relevant therapies. For example, Eylea's annual payment limits are multiplied by 2 because the recommended dosage per injection is double the HCPCS dosage. See Attachment D-6. Chart 9 below displays the annual payment limits of the four anti-VEGF treatments over time. See Attachment D-8.

Chart 9: Medicare Part B Payment Limit per Injection for Each Anti-VEGF Treatment, 2012 to 2021



(83) Avastin's payment limit per injection has historically been substantially lower than Eylea's. Medicare part B payment limits for Eylea and Avastin from 2012 to 2021 were approximately $1,929 and $9.00 per injection, respectively. See Attachment D-6.

(84) While the list price of Lucentis for wet AMD and RVO is larger than that of Eylea ($1,950 versus $1,850),[157] Lucentis' payment limit demonstrates that it has been subject to more substantial discounting over time than has Eylea. See Attachment D-6. This has resulted in the historic payment limit of Eylea being greater than the historic payment limit of Lucentis. Over the period from 2012 to 2021, the average of annual payment limits for Eylea and Lucentis were $1929 and $1,857, respectively. See Attachment D-6. Lucentis' annual payment limit has fallen approximately 20% since 2012, whereas Eylea's annual payment limit has declined only 6%.[158] See Attachment D-6. Over the same period, Lucentis' annual payment limit was $1,114 for DME and DR. See Attachment D-6.

(85) Moreover, physician surveys indicate that the price disparity between Eylea and its competitors has been a disincentive to prescribing Eylea.[159] Therefore, the fact that Eylea has achieved its position as a leader in its indicated

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157 Ex. 2229 (Regeneron, WAC Pricing File, 5/2021, at tab "Analysis").

158 $1,592 / $1,992 -1 = ~-20%; $1,836 / $1,961 -1 = ~-6%

159 Ex. 2278 (Regeneron, "Wave 1 2021 Performance Update: Wet AMD, DME, MEfRVO & DR w/out DME," 9/2021, at 97–106).

therapeutic areas despite these price disparities is a strong indication of the product's commercial success. Although higher-priced products could in principle incentivize physicians to prescribe those products rather than lower-priced alternatives because the higher-priced products would lead to the receipt of larger Medicare reimbursements, physician surveys and analyses of sales patterns demonstrate that this does not appear to be the case for Eylea.[160]

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[160] Ex. 2278 (Regeneron, "Wave 1 2021 Performance Update: Wet AMD, DME, MEfRVO & DR w/out DME," 9/2021, at 97–106).

Ex. 2220 (Manning (2015), at 241). ("This is inconsistent with the hypothesis that the major factor driving product choice between these two products is a simple financial motivation on the part of the physician or the manufacturer. Rather, it is consistent with the notion that physicians typically exercise medical judgment or are responsive to other factors on a patient-by-patient basis.")

9. Dosing Regimen is an Important Driver of Demand for Eylea

(86) The eye diseases treated by Eylea and the other products discussed here impose a very large cost on patients. Loss of vision is one of the most serious health insults an individual can experience, imposing substantial physical, social, and economic burdens on individuals.[161] Adults with vision impairment often have lower rates of workforce participation and higher rates

[161] Ex. 2167 (Centers for Disease Control and Prevention, "Vision Loss: A Public Health Problem," 6/12/2020, https://www.cdc.gov/visionhealth/basic_information/vision_loss.htm). ("People with vision loss are more likely to report depression, diabetes, hearing impairment, stroke, falls, cognitive decline, and premature death. Decreased ability to see often leads to the inability to drive, read, keep accounts, and travel in unfamiliar places, thus substantially compromising quality of life. The cost of vision loss, including direct costs and lost productivity, is estimated to exceed $35 billion.")

of depression and anxiety.[162] In older adults, vision impairment can contribute to social isolation, difficulty walking, and a higher risk of falls and fractures.[163] Hence, a treatment that meaningfully diminishes the likelihood of vision loss or that extends the time until vision deteriorates is something on which most consumers would place a very high value. As discussed previously, it turns out that the treatments that allow this good outcome (delayed or diminished vision loss) are unavoidably bundled with a "bad" characteristic—having an injection into the eye.

(87) Again, as discussed in Section 4, economic theory predicts that, all else the same, patients would be more likely to choose a treatment that provides a given therapeutic response with fewer, or less frequent injections. This is further supported by evidence that alleviation of treatment burden through extended dosing was an unmet need, that the patented dosing regimen has been a key differentiator for Eylea as compared to other treatment options,

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[162] Ex. 2269 (World Health Organization, "Blindness and Vision Impairment Fact Sheet," 10/14/2021, at 3, available at: https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment).

[163] Ex. 2269 (World Health Organization, "Blindness and Vision Impairment Fact Sheet," 10/14/2021, at 3).

and that a large share of physicians state they use Eylea according to the patented dosing regimen.

9.1. Eylea's patented dosing regimen addressed an unmet need for longer dosing intervals

(88) Frequent dosing of therapies to treat the relevant angiogenic eye disorders places a significant treatment burden on patients and physicians. For example, following the approval of Beovu to treat wet AMD in Canada, a Yahoo finance article citing Doug Earle, president and CEO of Fighting Blindness Canada, noted the difficulty patients have keeping up with frequent appointments, especially for those living in remote or isolated communities or requiring mobility assistance.[164] The article acknowledges the potential for

[164] Ex. 2270 (Yahoo Finance, "Beovu Now Publicly Reimbursed in Ontario and New Brunswick for the Treatment of Neovascular (Wet) Age-Related Macular Degeneration," 12/17/2021, https://finance.yahoo.com/news/beovu-brolucizumab-injection-now-publicly-120000109.html).

wet AMD to have a "devastating impact on patients and their vision if patients don't adhere to the regular treatment that is required[.]"[165]

(89) Frequent dosing, and the risk of significant harm to vision if doses are missed, represents a significant treatment burden for patients with the relevant angiogenic eye disorders. Physicians identified the need to alleviate this treatment burden as an unmet need in treating these disorders prior to the launch of Eylea. For example, a 2009 survey conducted by the ASRS asked participants to identify the (then-) current unmet need in the treatment of wet AMD.[166] 62.73% of survey respondents cited both improvement in visual outcomes and reduction in the frequency of injections (while maintaining visual acuity) as unmet needs, while 33.56% cited reduction of injection

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[165] Ex. 2270 (Yahoo Finance, "Beovu Now Publicly Reimbursed in Ontario and New Brunswick for the Treatment of Neovascular (Wet) Age-Related Macular Degeneration," 12/17/2021).

[166] Ex. 2259 (American Society of Retina Specialists, "Preferences and Trends Membership Survey," 2009, at 92).

frequency (while maintaining visual acuity) as the only unmet need.[167] In other words, 96.29% of participants identified reducing injection frequency as one of the key unmet needs in the treatment of wet AMD in 2009.[168]

(90) A Regeneron marketing strategy presentation from September 2011 identified [redacted][169] The presentation further identified [redacted].[170]

[167] Ex. 2259 (American Society of Retina Specialists, "Preferences and Trends Membership Survey," 2009, at 92).

[168] 33.56% + 62.73% = 96.29%.

[169] Ex. 2277 (Regeneron, "Marketing Planning Process," 9/2011, at 9).

[170] Ex. 2277 (Regeneron, "Marketing Planning Process," 9/2011, at 10).

(91) ATU surveys conducted in 2012 and 2013 also show that [redacted]. The 2012-Q4, 2013-Q2, and 2013-Q3 ATU surveys asked participants [redacted]?[171] In 2012-Q4, practitioners responded that [redacted].[172] Further, practitioners stated that [redacted].[173] Taken together, [redacted].[174]

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171 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 25).

Ex. 2163 (Regeneron, "Physician ATU: Wave 4," 8/6/2013, at 24).

Ex. 2140 (Regeneron, "Physician ATU: Wave 5," 11/2013, at 25).

172 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 25).

173 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 25).

174 [redacted]

(92) These survey responses demonstrate that less frequent dosing was an unmet need prior to the launch of Eylea and its patented dosing regimen and that longer dosing intervals remain an important consideration for physicians when selecting treatments for their patients. The ongoing need for increased dosing intervals means that the patented dosing regimen would be a relevant consideration for physicians and patients selecting treatment options when Eylea was first introduced and has remained so in the years since its introduction.[175]

9.2. Eylea's patented dosing regimen is a key differentiating factor

(93) As compared to other anti-VEGF treatments available for the relevant diseases, Eylea's patented dosing regimen is a key differentiating factor. I

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[175] Ex. 2050 (Brown Declaration, 2/10/2022, at ¶¶ 160–173).

Dr. Brown has provided descriptions of various efforts to extend the dosing regimens for treatments available prior to Eylea's launch, including Lucentis and Macugen, as well as more recent attempts including Conbercept. Since Eylea's launch, attempts to develop new treatments have sought to extend the dosing interval relative to Eylea's patented dosing schedule (rather than seeking to extend the dosing interval relative to the 4-week interval recommended for Lucentis).

understand that when seeking initial FDA approval for wet AMD, clinical testing of Eylea sought to show "non-inferiority" as compared to Lucentis (i.e., that Eylea and Lucentis had similar efficacy) using an extended dosing according to the '338 Patent.[176] Evidence that the patented dosing regimen is a key differentiating factor for Eylea is discussed below.

9.2.1. Regeneron has promoted the patented dosing schedule and credits it as a key factor causing commercial success

(94) Regeneron's marketing efforts for Eylea have included efforts to market the treatment's patented dosing schedule. This can be seen from Regeneron's marketing plans and promotional materials.

- A September 2011 internal marketing strategy presentation discussed Regeneron's strategy for positioning the Eylea brand. The presentation stated "[redacted]"[177]

[176] Ex. 2050 (Brown Declaration, 2/10/2022, at ¶¶ 75–78).

[177] Ex. 2277 (Regeneron, "Marketing Planning Process," 9/2011, at 15).

- An online ad for Eylea emphasizes its "Dosing Flexibility" for wet AMD patients.[178] The ad highlights Eylea's ability to be dosed at 8 weeks or longer following the initial loading doses as well as Eylea's ability to be dosed at 12 weeks after 1 years of effective therapy.[179]
- A Regeneron presentation meant for an external facing audience showcased the results of Eylea's clinical studies, VIEW1 and VIEW2.[180] Regeneron stated that 2 mg of Eylea dosed at every 8 weeks is clinically equivalent to the industry standard at the time, Lucentis's 0.5 mg dose every 4 weeks. [181] In addition, Regeneron notes that monthly injections pose challenges for patients as each office visit can be quite lengthy.

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[178] Ex. 2190 (Eylea Website, Wet AMD: Dosing Flexibility, https://hcp.eylea.us/about/wet-amd-dosing/ (accessed 1/5/2022)).

[179] Ex. 2190 (Eylea Website, Wet AMD: Dosing Flexibility (accessed 1/5/2022)).

[180] Ex. 2139 (Regeneron, "For the Treatment of Wet Age-Related Macular Degeneration," c. 2012).

[181] Ex. 2139 (Regeneron, "For the Treatment of Wet Age-Related Macular Degeneration," c. 2012, at 31.

Regeneron states that there is time lost from travel and from work for patients and their adult caregivers.[182]

- A 2013 advertisement for Eylea uses the phrase "Time Between Treatments" as a slogan for Eylea.[183] This phrase is followed by important prescribing information that mentions Eylea is dosed once every 8 weeks.[184] In addition, the page's background consists of an April and June calendar that are separated and in between them is a vial of Eylea.[185]
- A similar 2013 advertisement for Eylea shows October and December calendars separated by the image of an elderly lady and a child sharing a story. This image speaks to Eylea's ability to provide patients with a better quality of life has it can be dosed every two months instead of monthly, resulting in less time in the clinic.[186]

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182 Ex. 2139 (Regeneron, "For the Treatment of W)et Age-Related Macular Degeneration," c. 2012, at 13).

183 Ex. 2136 (Regeneron, Eylea Marketing Material, c. 2013).

184 Ex. 2136 (Regeneron, Eylea Marketing Material, c. 2013).

185 Ex. 2136 (Regeneron, Eylea Marketing Material, c. 2013).

186 Ex. 2137 (Regeneron, Eylea Marketing Material, 11/2013, at 29).

Screenshot: Eylea Ad[187]

- Regeneron marketing materials from 2013 characterized Eylea as "The Only VEGF Inhibitor Approved for Every 2-months Dosing Following 3 Initial Monthly Doses[.]"[188] This phrase was included as a page heading throughout the marketing materials, demonstrating the importance to

187 Ex. 2137 (Regeneron, Eylea Marketing Material, 11/2013, at 29).

188 Ex. 2137 (Eylea, Eylea Marketing Material, 11/2013 at 8–30).

Regeneron of conveying this statement about Eylea's unique dosing regimen.[189]

Screenshot: Eylea Marketing Material[190]

189 Ex. 2137 (Eylea, Eylea Marketing Material, 11/2013 at 8–30).

190 Ex. 2137 (Eylea, Eylea Marketing Material, 11/2013, at 8–30).

9.2.2. Regeneron ATU surveys show that dosing interval has been an important driver of Eylea prescribing

(95) After launching Eylea in late 2011, Regeneron began using ATU survey data to understand the opinions of physicians prescribing anti-VEGF products. Regeneron's ATU surveys provide insight into the importance of Eylea's recommended eight-week dosing schedule. These ATU surveys include results demonstrating that the treatment burden and dosing intervals were important to physicians and that practitioners viewed Eylea as a product that would improve treatment burden.

(96) Physician survey results illustrate that physicians [redacted].

- The 2012-Q4 ATU survey asked participants: "[redacted]"[191] The [redacted] cited by physicians, with [redacted] of participants [redacted] and [redacted] of participants [redacted]. Regeneron's

[191] Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 13).

own analysis of this data found "[redacted]"[192]

- The 2014-Q2 ATU DME Survey asked participants: "[redacted]" [redacted] with [redacted] of respondents [redacted] and [redacted] of respondents [redacted].[193] Further, when physicians were asked [redacted], [redacted] of respondents [redacted] and only [redacted] of respondents [redacted].[194] This demonstrates the unique role [redacted] driving the prescribing behavior for Eylea in comparison to Lucentis.
- The 2012-Q4 ATU survey asked practitioners [redacted]

192 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 13).

193 Ex. 2205 (Regeneron, "DME Market Assessment," 8/2014, at 46).

194 Ex. 2205 (Regeneron, "DME Market Assessment," 8/2014, at 46).

[redacted][195]

[redacted]. [redacted] of practitioners [redacted]; and [redacted] of practitioners [redacted].[196]

- Regeneron's internal presentation summarizing the 2011-Q3 ATU survey states: "[redacted]"[197] The survey presentation further states Eylea

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195 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 34).

Ex. 2208 (Regeneron, "Eylea MD ATU – Wave 2 Final Questionnaire," 12/19/2012, at 3).

196 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 34).

Another highly-rated attribute (with 86% of practitioners scoring 8, 9, or 10) was "better quality of life," which likely is impacted by treatment burden (among other things).

197 Ex. 2197 (Regeneron, "Physician ATU – Benchmark Wave," 9/15/2011, at 2).

"[redacted]"[198]

- The 2012-Q4 ATU survey asked participants to [redacted][199] [redacted].
  - For physicians [redacted], [redacted].[200] In other words, [redacted]

198 Ex. 2197 (Regeneron, "Physician ATU – Benchmark Wave," 9/15/2011, at 36).

199 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 23, 24).

200 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 23, 24).

[redacted]. This was the largest percentage point difference among the included options.[201]

- Similarly, for physicians [redacted], [redacted] of respondents [redacted], whereas only [redacted] who [redacted].[202] This was the [redacted].[203]

(97) These results demonstrate that physicians are aware of the burdens that more frequent dosing puts on their patients and take dosing interval into account when selecting treatment options. Further, physicians provided these responses to surveys taken during the years immediately following Eylea's

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201 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 23, 24).

202 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 23, 24).

203 Ex. 2138 (Regeneron, "Physician ATU: Wave 2," 2/2013, at 23, 24).

Cost/Reimbursement options were the largest percentage point difference, at 70% ("Cost / Reimbursement (NET)") and 65% ("Cost"). However, both of these differences favored Avastin (i.e., Cost was more a reason to switch to Avastin than to Eylea).

launch, meaning that dosing interval was identified as an important driver of physician choice over precisely the same time period that Eylea was experiencing rapid growth in share of sales. See Section 8.3. These responses, and their overlap with Eylea's rapid sales growth, demonstrate that the patented dosing interval was an important driver of Eylea's commercial success.

9.2.3. Members of the ASRS identified Eylea as allowing the longest treatment interval

(98) The ASRS conducts annual surveys of its members, referred to as the Preferences and Trends (PAT) survey. From 2014 – 2016, the PAT surveys included questions asking respondents, in their experience, which anti VEGF treatments allowed for the longest treatment intervals. The responses demonstrate that Eylea's longer dosing interval is a differentiating factor relative to Avastin and Lucentis.

- The 2014 PAT survey asked "[redacted]"[204]

[204] Ex. 2250 (American Society of Retina Specialists, "Preferences and Trends (PAT) Survey," 2014, at 58).

- The 2015 and 2016 PAT surveys asked "[redacted]"[205]

(99) Table 6 below presents responses, both in the U.S. and internationally. For each of these years, Eylea is identified by a majority of respondents (both from the U.S. and internationally), with neither Avastin nor Lucentis exceeding 10%. See Table 6.

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[205] Ex. 2244 (American Society of Retina Specialists, "Preferences and Trends (PAT) Survey," 2015, at 70).

Ex. 2243 (American Society of Retina Specialists, "Preferences and Trends (PAT) Survey," 2016, at 58).

The 2015 survey omitted the word "agent" and the italicized the word "most" from the question.

Table 6: Share of Respondents Identifying [redacted][206]

[redacted]

206 Ex. 2250 (American Society of Retina Specialists, "Preferences and Trends (PAT) Survey," 2014, at 59).

Ex. 2244 (American Society of Retina Specialists, "Preferences and Trends (PAT) Survey," 2015, at 70).

Ex. 2243 (American Society of Retina Specialists, "Preferences and Trends (PAT) Survey," 2016, at 59)).

9.2.4. Regeneron public statements demonstrate the importance of the patented dosing schedule to Eylea's commercial success

(100) Regeneron public statements near the time of Eylea's launch further demonstrate the importance of the patented dosing schedule to Eylea's commercial success. Such statements, contained in earnings call transcripts, show Regeneron's view that commercial success of Eylea would (and did) depend on its ability to communicate the benefits of the patented dosing schedule.

- In the 2011-Q4 Regeneron earnings call, Regeneron's CEO Leonard Schleifer stated, "We believe that Eylea with [its] less frequent dosing offers a much more attractive new treatment option that provides an important alternative to wet AMD patients and physicians."[207] Dr. Schleifer also stated the decreased monthly dosing has strongly resonated with the AMD community.[208]

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[207] Ex. 2133 (Regeneron, Earnings Call Transcript, 2/13/2012, at 3).

[208] Ex. 2133 (Regeneron, Earnings Call Transcript, 2/13/2012, at 3). ("The benefit of less than monthly dosing with efficacy that is clinically equivalent to

- During Regeneron's 2012-Q1 earnings call, one of Regeneron's executives stated that some of Eylea's highest use had come from people living in rural areas as their traveling burden for appointments makes the eight-week dosing more appealing.[209]
- During the 2012-Q2 Regeneron earnings call, one of Regeneron's executives stated that Eylea's convenience of less than monthly dosing (along with its efficacy) was contributing to Eylea's strong wet AMD sales.[210]

9.3. Eylea is more effective at treating patients with worse visual acuity, which imparts a downward bias to its observed treatment interval

(101) As discussed above, Eylea has recommended dosing practices with extended dosing relative to prior treatments. Indeed, Dr. Do has indicated that

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monthly ranibizumab appears to have resonated strongly with the AMD community, as has our pricing.")

209 Ex. 2134 (Regeneron, Earnings Call Transcript, 4/26/2012, at 9). ("I think some of our highest utilization, however, is in more rural areas where people have to travel far for their appointments and so the every eight week dosing is appealing in those types of settings.")

210 Ex. 2135 (Regeneron, Earnings Call Transcript, 7/25/2012, at 6).

physicians commonly seek to treat patients on an 8-week interval (or longer) during the maintenance phase of treatment for all angiogenic eye disorders.[211]

(102) With that said, clinical evidence has shown that Eylea (aflibercept) is more effective at improving vision among patients suffering from DME with worse initial visual acuity.[212] As a result, physicians have an interest in treating patients with more serious disease with Eylea, and those patients on average may require more frequent dosing because of the severity of their condition.[213]

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211 Ex. 2051 (Do Declaration, 2/10/2022, at ¶ 138).

212 Ex. 2102 (Wells, John A., et al. (2015), "Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema," *The New England Journal of Medicine* 372(13): 1193–1203, at 1193). ("At worse levels of initial visual acuity, aflibercept was more effective at improving vision.")

213 Ex. 2102 (Wells (2015) at 1195). ("The study drugs were injected into the study eyes at baseline and then every 4 weeks unless visual acuity was 20/20 or better with a central subfield thickness below the eligibility threshold and there was no improvement or worsening in response to the past two injections.")

Thomas Albini, Dep Tr., 1/20/2022, at 37:7–40:16, 62:20–70:7, 72:3–9, 72:21–73:20.

(103) Data on physician switching behavior demonstrates this dynamic. For patients that are started on either Avastin or Lucentis, Eylea is likely to be the second treatment used if the physician decides to switch treatments. Regeneron documents show that [redacted] of patients with wet AMD are initially treated with Avastin.[214] Meanwhile, Eylea's patient share for second line of therapy is [redacted], [redacted], and [redacted] for wet AMD, DME, and DR, respectively.[215]

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[214] The data shown is sourced through IQVIA. IQVIA provides a variety of data and analytics services to the life sciences industry. As part of their business IQVIA offers a variety of pharmaceutical and healthcare related data. See:

Ex. 2206 (IQVIA, Form 10-K, 2020, at 5).

Ex. 2207 (IQVIA Website, Available IQVIA Data, https://www.iqvia.com/insights/the-iqvia-institute/available-iqvia-data (accessed 1/18/2022)).

Ex. 2274 (Regeneron, "Eylea Wet AMD Line of Therapy Insights," 4/2020, at 3).

[215] Ex. 2278 (Regeneron, "Wave 1 2021 Performance Update Wet AMD, DME, MEfRVO, and DR w/out DME," 9/2021, at 78, 81, 90).

(104) This means that even though Eylea is generally used with longer dosing intervals than Avastin or Lucentis for a given patient, for patients overall dosing intervals for Eylea would be even longer if all patients had equal severity of conditions.

The next highest share of second line therapy is [redacted] (Lucentis), [redacted] (Lucentis), and [redacted] (Avastin) for wet AMD, DME, and DR, respectively.

10. Eylea's Commercial Success Cannot be Explained by Factors Not Related to the Claimed Methods of Treatment

(105) Various other factors and attributes aside from dosing can contribute to a product's economic success, including other product attributes; the competitive environment facing the product; marketing efforts; pricing; and discount and rebate practices; etc. However, a review of the marketing efforts, pricing, and discount/rebate practices in this case demonstrates that Eylea's commercial success cannot be explained by these factors. The totality of evidence further supports the conclusion that the claimed dosing regimen has been an important factor contributing to Eylea's commercial success.

10.1. Regeneron's marketing efforts have been limited and have included promotion of the patented dosing regimen

(106) The economic purpose of marketing prescription medicines is intended to inform potential prescribers, and often potential patients, about innovations in healthcare treatment.[216] Economic theory indicates that biopharmaceutical companies engage in promotional activities because informing (and reminding) prescribers and patients about treatment options is effective at

[216] Ex. 2260 (Schweitzer, Stuart (2007), *Pharmaceutical Economics and Policy*, 2nd ed., New York: Oxford University Press, at 82).

increasing product utilization.[217] However, Eylea's marketing efforts have been consistent with industry marketing levels. In other words, Eylea's success is not attributable simply to excessive marketing.

(107) Because of the economic importance of informing prescribers and patients about new medicines, a meaningful share of pharmaceutical companies' resources is typically dedicated to marketing. Gagnon and Lexchin (2008) reviews a number of sources estimating that U.S. pharmaceutical companies

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[217] Ex. 2178 (Donohue, Julie, Ernst R. Berndt (2004), "Effect of Direct-to-Consumer Advertising on Medication Choice: The Case of Antidepressants," *Journal of Public Policy & Marketing* 23(2): 115–127, at 116, 117). ("Another study of antiulcer medications finds that product marketing to physicians increases sales for the advertised product…")

Ex. 2177 (Donohue, Julie et al. (2007), "A Decade of Direct-to-Consumer Advertising of Prescription Drugs," *The New England Journal of Medicine* 35(7): 673–681, at 673). ("Evidence suggests that direct-to-consumer advertising of prescription drugs increases pharmaceutical sales…")

spend between 22.5% and 33.0% of their sales revenue on marketing.[218] Their own estimate is that promotional expenditures as a percent of total U.S. sales is about 24.4%, including the cost of product sampling.[219] If product sampling costs are excluded, marketing expenditures are about 17.7% of total U.S. sales.[220]

(108) Based on these ratios, Regeneron spent relatively little on marketing for Eylea relative to the biopharmaceutical industry generally. Regeneron's commercial P&L includes line items "External Expenses" and "People Expenses."[221] I understand that the "External Expenses" line item includes Regeneron's marketing expenditures for Eylea and the "People Expenses" line item refers to the labor expenses (e.g., salaries, benefits, and other employment costs) for

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218 Ex. 2196 (Gagnon, Marc-Andre and Joel Lexchin (2008), "The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States," *PLoS Medicine* 5(1): 29–33, at 32).

219 Ex. 2196 (Gagnon (2008), at 32).

220 ($57.5 billion − $15.9 billion) / ($235.4 billion) = ~17.7%. See:

Ex. 2196 (Gagnon (2008), at 30, 32).

221 Ex. 2200 (Regeneron, "U.S. Eylea Historical Brand P&L," 5/2021, at 2).

Regeneron employees who spend part or all of their time working on the Eylea product.[222]

(109) Consistent with what would be expected, Regeneron made large initial investments in marketing Eylea in 2011. Regeneron launched Eylea in November 2011, incurring [redacted] in external expenses and [redacted] in people expenses during 2011. See Attachment D-3. Following these expenditures during Eylea's launch year, from 2012 through 2020, Regeneron's external expenses on Eylea never exceeded more than [redacted] of net sales and people expenses never exceeded more than [redacted] of net sales, both in 2012 (i.e., the first full year Eylea was available). See Attachment D-3. Since launch, Regeneron's total external expenditures have been [redacted], or [redacted] of net sales, while total people expenditures have been [redacted], or [redacted] of net sales. See Attachment D-3.

(110) These total expenditures are significantly smaller as a share of net sales than the industry average range of 22.5% to 33% for marketing expenditures[223] Further, even if one compares the smallest Gagnon and Lexchin's estimate

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[222] Conversation with Regeneron Executive Director, Commercial Finance & Business Planning and Senior Director, FP&A.

[223] Ex. 2196 (Gagnon (2008), at 32).

against Eylea's highest spending year after its launch year, Eylea's marketing expenditures are still substantially below the percentage for the pharmaceutical industry as a whole. The Gagnon (2008) estimate (excluding samples) is equal to 17.7% of net sales, which is approximately [redacted] percentage points larger than Eylea's marketing spend of [redacted] of net sales in 2012.

(111) These values suggest Regeneron was able to spend less on advertising efforts than industry averages. In view of this relatively limited expenditure, it is highly unlikely that Regeneron's marketing efforts (rather than the patented dosing regimen) could have driven Eylea's commercial success. These comparisons further support a conclusion that the product's features (including its patented dosing regimen), rather than marketing efforts, were important factors driving commercial success.

10.2. Regeneron has had limited discounting and rebate programs

(112) In addition to the marketing efforts, Regeneron, like virtually any company selling innovative medicines, has implemented rebate and discounts as part of its commercialization of Eylea. Rebate, discount, and other price reduction activities are common in the pharmaceutical industry, and analyses of Regeneron's discounting practices demonstrate that they were unlikely to have been a key factor driving Eylea's commercial success.

(113) Over the period from 2011 to 2021, Regeneron's rebates and discounts for Eylea have ranged from [redacted] to [redacted] of gross sales. See Attachment D-1. In total from 2011 to 2021, Regeneron's rebates equaled [redacted] of gross sales. See Attachment D-1. Although direct comparisons of rebate and discount magnitudes (and the impact of rebates and discounts) between Eylea and other anti-VEGF options are limited by data availability, several pieces of evidence suggest that these rebate and discounts were unlikely to have driven Eylea's rapid sales growth and sustained commercial success, as can be seen from comparisons with Lucentis.

- The extensive discounting practices of Lucentis can be seen in its declining Medicare payment limit over time. See Attachment D-6. As shown in Section 8.4, the payment limit of Lucentis has decreased by approximately 20% since 2012. In comparison the payment limit of Eylea has decreased by only 6%. See Section 8.4.
- Additionally, I understand that the discounts and rebates offered for Lucentis make Lucentis the first choice among some large practices that treat enough patients with relevant conditions to qualify for the largest

discounts and rebates.[224] I understand that both Regeneron and Genentech offer rebates to group purchasing organizations and off-invoice discounts, and that Regeneron estimates that historically the discounts and rebates offered for Lucentis have been approximately three times as large as those offered for Eylea.[225] For example, I understand at present that the largest discounts or rebates Regeneron offers for Eylea are approximately [redacted], whereas Regeneron estimates that the largest rebates and discounts offered for Lucentis are approximately [redacted].[226] I also understand that in recent years, Genentech has offered a third category of price reduction in the form of a loyalty program, whereas Regeneron does not offer such a program for Eylea.[227]

- Similarly, as compared to Avastin, the magnitude of Eylea's rebates has little impact on the price disparity between Eylea and Avastin. For

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224 Ex. 2275 (Regeneron, "Vestrum Anti-VEGF Market Share Adjustment Overview," 5/10/2019, at 2).

225 Conversation with Regeneron Senior Director, Market Access Strategy.

226 Conversation with Regeneron Senior Director, Market Access Strategy.

227 Conversation with Regeneron Senior Director, Market Access Strategy.

example, the highest annual value of aggregate reductions (which would not all apply for any individual sale of Eylea), [redacted], would reduce Eylea's list price to [redacted].[228] See Section 8.4. Such a reduction in price does not eliminate the disparity with Avastin, which is effectively priced under $10 per injection. See Section 8.4. This demonstrates that Eylea's price discounts are unlikely to have driven commercial success for Eylea over Avastin.

10.3. Regeneron's sampling program is unlikely to have driven Eylea's commercial success

(114) Regeneron offers Eylea samples to physicians upon request, primarily to physicians at private or community practices.[229] I understand that physicians generally use Eylea samples to provide treatment when insurance coverage is uncertain, for example when treating new patients with unclear coverage.[230]

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228 [redacted].

229 Conversation with Regeneron Associate Director, Field Force Effectiveness, Ophthalmology and Associate Director, Sample Operations and Accountability.

230 Conversation with Regeneron Associate Director, Field Force Effectiveness, Ophthalmology and Associate Director, Sample Operations and Accountability

Samples allow physicians to treat a patient with Eylea while insurance or other coverage is being determined.[231]

(115) Regeneron's sampling program has been limited and is unlikely to have driven Eylea's sales growth. Nor does sampling demonstrate that the patented dosing interval was not an important contributor to commercial success. As an initial matter, Regeneron achieved significant sales and sales growth prior to the introduction of a sampling program. Regeneron first offered product samples beginning in late 2013.[232] See Attachment D-5. These initial samples were offered after Eylea had already achieved a successful launch and captured a sales share of approximately [redacted] in its first two years available. See Section 8.3.2.

(116) Further, samples have never been a substantial portion of total unit sales of Eylea and hence are unlikely to have been a meaningful driver of commercial

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[231] Conversation with Regeneron Associate Director, Field Force Effectiveness, Ophthalmology and Associate Director, Sample Operations and Accountability

[232] Ex. 2169 (Regeneron, "Eylea Sample Disbursement 2013 to 2021," c. 2021, at tab "Knipper Eylea Distribution").

The first samples were dated in September 2013 and shipped in October 2013.

success. Since launching its sample program, Regeneron has provided [redacted] samples, which represents [redacted] of total historical Eylea unit sales. See Attachment D-4. From 2014 through 2020 (i.e., the full years that Regeneron has run a sampling program), sample units have ranged from [redacted] to total unit sales (in 2014) to [redacted] of total unit sales (in 2019). See Attachment D-4. Regeneron has provided [redacted] samples from 2014 through 2020, or [redacted] of unit sales during the same period. See Attachment D-4.

(117) In conclusion, the delay in starting a sampling program after launching Eylea and the low quantity of samples offered by Regeneron render them unlikely to have caused commercial success and hence further demonstrate that product attributes, such as the patented dosing regimen, have been more important factors driving Eylea's commercial success.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine, imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Dated: Feb 11, 2022

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Washington, D.C.