

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALVOTECH USA INC. and ALVOTECH HF,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case: PGR2025-00085
U.S. Patent No. 12,168,036

EXPERT DECLARATION OF DR. NEIL M. BRESSLER
IN SUPPORT OF PATENT OWNER RESPONSE

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I. Introduction and Assignment

1. I have been retained by counsel for Regeneron Pharmaceuticals, Inc. (“Regeneron”) as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions in connection with the Petition for Post-Grant Review (“PGR”) filed by Alvotech USA Inc. and Alvotech hf. (“Alvotech”) challenging claims 1-38 of Regeneron’s U.S. Patent No. 12,168,036 (the “’036 patent”) (“Petition”), including in response to the declaration of Dr. Donald D’Amico (Ex.1003) submitted in support of Alvotech’s Petition.

2. I submit this declaration in support of Regeneron’s Patent Owner Response (“POR”). I reserve the right to provide additional opinions in response to additional arguments or declarations offered by Alvotech.

3. In forming my opinions, I reviewed Alvotech’s Petition, the declarations of Dr. Donald Joseph D’Amico (Ex.1003) and Dr. Robert J. Falconer (Ex.1004) submitted in support thereof, all the materials cited in the Petition and Dr. D’Amico’s declaration, and all the materials cited herein or referred to in Appendix B. My opinions and views set forth below also are based on my decades of education, training, research, and experience in the field of ophthalmology.

4. I understand from counsel that Regeneron also has engaged Dr. Bernhardt Trout, an expert possessing the formulation-related qualifications set forth Dr. D’Amico’s definition of the person of ordinary skill in the art (“POSA”). I spoke

to Dr. Trout on June 10, 2026, and again on June 12, 2026. In those conversations, I summarized for him my opinions on this matter from the perspective of a clinician-POSA as of May 2018 and answered any questions he posed. I understand that Dr. Trout may take those conversations into account in rendering his own opinions, which I understand have been or will be set forth in a separate declaration. I have not reviewed Dr. Trout's declaration in any form.

5. Below I respond to certain of Dr. D'Amico's opinions as set forth in his declaration, as well as certain statements made by Alvotech in the Petition. I have not, however, undertaken to respond to every statement in Dr. D'Amico's declaration or every technical assertion in Alvotech's Petition. My silence as to any such opinion or assertion should not be understood to mean that I agree with it.

6. I am being compensated for my work in this case at the rate of \$1,100 per hour. I have no personal or financial stake in the outcome of the present proceeding. My compensation does not depend in any way on the outcome of this proceeding.

II. Qualifications and Experience

7. I am a Professor of Ophthalmology in the Department of Ophthalmology where I have been for 29 years, also known as the Wilmer Eye Institute, at the Johns Hopkins University School of Medicine, having been promoted to Professor in 1997, 9 years after starting on the full-time tenure track

faculty in 1988. I subsequently received an endowed professorship, the James P. Gills Professorship in Ophthalmology, in 2000. From 2005 to 2018, I served as Chief of the Retina Division of the Department of Ophthalmology at Johns Hopkins School of Medicine, and currently serve as a Director of one of only a few endowed Centers at the School of Medicine, the Yoovidhya Global AIRRE Center, dedicated to *Advanced Innovations in Retina Research and Education* at the Wilmer Eye Institute. As a physician-scientist, I have received numerous honors and awards from national and international ophthalmology societies in recognition of my expertise in retinal diseases, particularly in clinical trials related to diabetic retinopathy and macular degeneration. In addition to conducting my own research as Chair of numerous collaborative, multicenter, national, and international trials sponsored by the National Institutes of Health and industry, I also have served, since 2013, as Editor in Chief of *JAMA Ophthalmology*—one of the world’s top three peer-reviewed scientific journals in ophthalmology, as measured by impact factor. In 2025, the journal’s articles were accessed over 8 million times through full-text downloads and abstract views, and between 2023 and 2025, JAMA Ophthalmology published three of the top four most-cited original articles in the field, all contributing to its high impact factor.

8. Throughout my career, I have chaired numerous randomized clinical trials and published hundreds of peer-reviewed scientific articles not only in

ophthalmology journals but also in general medical journals such as the New England Journal of Medicine and JAMA (the Journal of the American Medical Association).

9. I also have testified before the U.S. House of Representatives Committee on retinal diseases as a medical expert. Additionally, during my tenure as Chair of the Diabetic Retinopathy Clinical Trials Network (“the Network”), the Network was formally recognized by the U.S. Congress—in House Resolution 36 (June 16, 2009), Senate Resolution 209 (July 7, 2009), and by the Senate Appropriations Committee (August 2010). The Network was also acknowledged as one of four priority research areas within the National Eye Institute in the Departments of Labor, Health and Human Services, and Education, and in the Related Agencies Appropriations Bill of 2012.

10. I graduated from the University of Michigan with a Bachelor of Science degree in 1978 and earned my medical degree from Johns Hopkins University School of Medicine in 1982.

11. After graduating from medical school and completing a one-year internship in the Department of Medicine at Johns Hopkins Hospital, I completed an ophthalmology residency at Harvard Medical School’s Massachusetts Eye and Ear Infirmary in 1986 and a medical retina fellowship at the Wilmer Eye Institute in

1987. From 1987 to 1988, I worked as a faculty member for Harvard Medical School, while continuing and completing my training in surgical retina.

12. I then joined the Retina Division of Johns Hopkins University School of Medicine (Department of Ophthalmology, Wilmer Eye Institute) as Assistant Professor in 1988. I was promoted to Associate Professor in 1991 and to Professor in 1997.

13. In 2000, I received the inaugural James P. Gills Professorship of Ophthalmology. From 2005 to 2018, I served as Chief of the Retina Division, which included 18 full-time retina physicians as well as over 50 clinical and 40 research staff.

14. In addition to my work at Johns Hopkins School of Medicine, I was the President of the Macula Society in 2013 and 2014, after serving as its Program Chair for nine years.

15. As a practicing ophthalmologist and retinal specialist with over 38 years of clinical practice, I am regarded by my peers as a leading expert in diabetic retinopathy and macular degeneration. I have evaluated and treated thousands of patients with diabetic retinopathy and the neovascular (“wet”) form of age-related macular degeneration (wAMD). I have administered thousands of anti-VEGF intravitreal injections to treat those conditions.

16. My expertise includes building best treatment management plans for individuals with diabetic retinopathy, the leading cause of irreversible blindness, if left untreated, in working-age adults, and wAMD, the leading cause of irreversible blindness, if left untreated, among older individuals in advanced economies. Currently, I continue to maintain an active national and international referral practice for retinal diseases.

17. My primary research interests for over 35 years have been designing, operating, administratively leading, and reporting results of clinical trials for common retinal diseases, including age-related macular degeneration and diabetic retinopathy. I have served as Chair and Principal Investigator of the Chair's Office for many multicenter randomized clinical trials, including three clinical trials in wAMD and related diseases sponsored by the National Eye Institute of the National Institute of Health (NIH), three multinational randomized clinical trials sponsored by the industry, one clinical trial in dry AMD sponsored by the industry, and seven other National Eye Institute sponsored randomized clinical trials in diabetic retinopathy, including diabetic macular edema.

18. To date, I have authored 500 peer-reviewed publications on a wide range of topics related to diagnosing and treating retinal diseases, including imaging of retinal diseases, treatment regimens of common retinal disease, reviews in *JAMA* and the *New England Journal of Medicine*, and more recently, cutting-edge AI

research in the field of retina. Specifically, in the areas of age-related macular degeneration and diabetic retinopathy, I have authored over 150 peer-reviewed clinical research publications in wAMD and over 150 in diabetic retinopathy, most of which were from randomized clinical trials, the apex of study designs for evidence-based medicine. For example, in diabetic retinopathy, clinical trials from the NIH-sponsored Diabetic Retinopathy Clinical Research Network not only defined the treatment regimen and management of diabetic macular edema and proliferative diabetic retinopathy but also were the basis of guidelines in the management of diabetic macular edema and proliferative diabetic retinopathy.

19. As a leader in clinical research, I have overseen research and publications in the field of ophthalmology and beyond. Since 2013, I have been the Editor in Chief of *JAMA Ophthalmology* and a member of the *JAMA Network* Editorial Board. *JAMA Ophthalmology* is one of the foremost peer-reviewed medical journals that covers all aspects of ophthalmology. It is published by the American Medical Association, whose affiliation dates back to 1929, and I am its ninth Editor in Chief. Over the past several years while I have been the Editor in Chief, the articles published by *JAMA Ophthalmology* have had millions of views and downloads, and related podcasts separately had thousands of downloads. *JAMA Ophthalmology* also is mentioned in mainstream news and social media more than any other ophthalmology journal in the world.

20. Since 2003, I also have served on the National Eye Institute's Data and Safety Monitoring Committee for intramural clinical trials, where I have been, and currently am, Chair for over 20 years. The Committee ensures the safety of study participants in clinical trials sponsored by the intramural program of the National Eye Institute by providing oversight and feedback to investigators in the design, operation, and reporting of clinical trial outcomes, reporting directly to the Director of the National Eye Institute of the National Institute of Health.

21. From 2006 to 2012, I served as Chair of the NIH-sponsored Diabetic Retinopathy Clinical Research Network, the largest ophthalmology network of multicenter randomized clinical trials. In that role, I was responsible for establishing guidelines, policies, and protocols for conducting retina-related clinical research and for implementing them, fostering academic integrity and optimal clinical trial performance. During my time, the Network successfully completed 20 studies, including randomized clinical trials sponsored by the National Eye Institute. These studies have been instrumental in shaping clinical practice guidelines in diabetic retinopathy and diabetic macular edema around the world. The Network, as a whole, included over 100 ophthalmology clinical sites and over one thousand investigators and study personnel across the United States.

22. I served on the FDA Ophthalmic Devices Panel for 24 years, through 2024, including two terms as Chair from 2008 to 2011 and again from 2019 to 2022.

The Ophthalmic Devices Panel reviews and evaluates the safety and effectiveness of investigational and marketed devices intended for use in the eyes. The panel then makes appropriate recommendations to the FDA Commissioner on whether the benefits of these devices outweigh the risks to patients—a crucial consideration in FDA approval decisions.

23. In addition to research and clinical practice, I have supervised 97 ophthalmologists specializing in retina, termed retina fellows or advanced specialty training programs physicians, as well as over 185 ophthalmology residents, and mentored retina specialists in clinical research, many of whom became leaders in retina practices, retina societies, and department chairs both within the United States and internationally. I have been the Program Director for Continuing Medical Education meetings at Johns Hopkins University, annually, since 1989. I also serve as the Program Director for two to three annual Continuing Medical Education meetings for Johns Hopkins University, which recently have had more than 1,000 on-line registrants each year. In this role, I develop programs directed to teaching the latest treatment regimens and clinical studies in wAMD and diabetic retinopathy. I also have lectured at numerous institutions and society meetings around the world on treating wAMD and diabetic retinopathy and received over 25 national and international awards in ophthalmology in Asia, Europe, North America, and South America.

24. A current copy of my curriculum vitae is included as Appendix A and sets forth my qualifications and experience in further detail.

III. Legal Standards

25. I am not an expert in the law. The legal standards I have applied were explained to me by counsel for Patent Owner.

A. Obviousness Generally

26. I have been informed that a patent claim may be invalid for obviousness if the differences between the claimed invention and the prior art are such that the subject matter as whole would have been obvious to a person of ordinary skill in the art (“POSA”) at the time the invention was made.

27. I also am informed that in evaluating obviousness, I should consider the following factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the pertinent art; (4) any objective indicia of non-obviousness, including unexpected results, commercial success, long-felt but unresolved needs, failure of others, skepticism of others about the invention, and later praise of that invention.

B. Motivation

28. I have been informed that, when a party challenging a patent relies on multiple references to demonstrate that an invention would have been obvious to the POSA, the challenger must prove not only that the prior art as a whole taught or suggested the invention, but also that the POSA would have had reason to select the

prior art references on which the challenger relies and to combine the teachings of the prior art references in a manner that would have arrived at the claimed invention. In other words, there needs to be a reason to combine the known elements in the way claimed by the invention.

C. Expectation of Success

29. I understand from counsel that, in addition to having a motivation to achieve the claimed invention, the POSA who is following the reference or references that purportedly make it obvious must have had a reasonable expectation of success in practicing the invention to solve the POSA's goals. I understand from counsel that to have a reasonable expectation of success, one must have been motivated to do more than merely vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

D. Prohibition on Use of Hindsight

30. I have been informed that obviousness must be assessed based on the knowledge possessed by the POSA at the time when the invention was made. In other words, it is impermissible to use hindsight-based knowledge of the claimed invention to determine questions of obviousness. Relatedly I understand that the inventor's path itself never leads to a conclusion of obviousness; that is hindsight.

What matters is the path that the POSA would have followed, as evidenced by the pertinent prior art.

31. I am informed that the law recognizes that patentable inventions often can be characterized as new combinations of preexisting principles or features. I am informed that the directive for the POSA to consider the invention “as a whole” is a guardrail against the use of hindsight, because it prohibits the POSA from breaking the claimed invention down into parts, and using the claimed invention as a roadmap to find all of its parts in the prior art.

E. Teaching Away

32. I have been informed that references that “teach away” from the claimed invention—in other words, references that would lead the POSA in a different direction from that taken by the inventor—must be considered. I also understand that a prior art reference teaches away from the claimed invention if the POSA, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that would lead to the claimed invention. I understand that in general, a reference will teach away if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of a result sought by the claimed invention. In determining whether the claimed invention would have been obvious, one must

consider the prior art as a whole, and must consider any individual reference for its whole disclosure.

F. Obviousness and Ranges

33. I am informed that if a claimed invention falls within the range of the values disclosed in prior art, the inquiry becomes whether there would be motivation to select the claimed value within those prior art ranges. I am further informed that the disclosure of a range in prior art does not disclose the endpoints of the range or other discrete points within it, and that a wide prior art range does not render a much narrower range obvious. In determining whether there would be motivation to select the claimed value, one must carefully consider contextual characteristics and whether a POSA would have had motivation to carry out that specific optimization. In particular, I understand that the number of differences from the prior art or the relationship between those differences informs whether a POSA would be motivated to make that combination and with a reasonable expectation of success.

34. Furthermore, I understand that the disclosure of a range can make the claimed value obvious only when a POSA would recognize that value as one that could affect a particular result, and only when the range is not so broad that it encompasses a very large number of possible values, such that the range does not teach any specific values or combinations. I am informed that even if these conditions are satisfied, evidence of teaching away, unexpected results, or other

secondary considerations can rebut that initial showing of obviousness. I am further informed that in cases of overlapping ranges involving multiple components, evidence that variables interact in unpredictable or unexpected ways can make that combination non-obvious.

IV. The '036 Patent

35. The '036 patent relates to ophthalmic formulations containing high concentrations of VEGF receptor fusion protein, at least about 8 mg, in a volume of about 100 microliters or less, with pharmaceutically suitable viscosity and particularly suited for intravitreal administration. The specification explains that “[a]nti-VEGF therapeutics, administered via intravitreal injection, are currently the standard of care for treatment of neovascular age-related macular degeneration, diabetic macular edema, and retinal vascular occlusive disease.” Ex.1001 at 51:19-22. However, “[t]here is a pressing need for more effective and durable therapies in clinical practice,” as “monthly or bi-monthly intravitreal injections represent a significant treatment burden on patients, caregivers, and physicians.” Ex.1001 at 51:22-26. The '036 patent describes high-concentration ophthalmic formulations of VEGF receptor fusion proteins (primarily aflibercept) that satisfy this “pressing need,” and methods of using them to treat angiogenic eye disorders.

36. The '036 patent defines “angiogenic eye disorders” as “any disease of the eye which is caused by or associated with the growth or proliferation of blood

vessels and/or by blood vessel leakage.” Ex.1001 at 29:19-22. The non-limiting examples of conditions treatable and preventable by using the claimed formulations and methods include “age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathies [and] [d]iabetic retinopathy in a patient who has diabetic macular edema (DME).” Ex.1001 at 29:22-51.

37. The '036 patent reports animal studies showing that “the high dose VEGF Trap (140 mg/ml) formulations tested were well tolerated in normal New Zealand White rabbit eyes within 12 weeks post-single intravitreal administration. After a single intravitreal injection of 7 mg of VEGF Trap, no signs of abnormalities or inflammation were seen in the fundus,” Ex.1001 at 51:55-61, and that “vascular leak inhibition in the retinas of animals receiving higher doses of aflibercept lasted longer than that of animals receiving lower doses,” Ex.1001 at 58:39-43. The '036 patent cites human clinical trials involving Eylea® 2mg, including CLEAR-IT 1, CLEAR-IT 2, VIEW studies, and Da Vinci. Ex.1001 at 8-9. And it cites a 2021

Regeneron press release involving Eylea® 8 mg announcing “encouraging topline phase 2 data.” Ex.1001 at 8.

A. Challenged Claims

38. The '036 patent includes 38 claims, which I have reproduced below.

1. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20° C.

2. The method of claim 1 wherein, following said intravitreal injection, the subject maintains or achieves a reduction in central retinal thickness but does not experience a significant increase in blood pressure.

3. The method of claim 1 wherein, following said intravitreal injection, the subject maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure.

4. The method of claim 1, wherein the viscosity is about 10-13 cP at 20° C.

5. The method of claim 1, wherein the viscosity is about 11-12 cP at 20° C.

6. The method of claim 1, wherein the viscosity is about 12-15 cP at 20° C.

7. The method of claim 1, wherein the viscosity is about 5 cP at 20° C.

8. The method of claim 1, wherein the viscosity is about 6 cP at 20° C.
9. The method of claim 1, wherein the formulation comprises a sugar.
10. The method of claim 1, wherein the formulation comprises sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol.
11. The method of claim 1, wherein the formulation comprises an amino acid.
12. The method of claim 1, wherein the VEGF receptor fusion protein is aflibercept.
13. The method of claim 1, wherein the angiogenic eye disorder is age- related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy.
14. The method of claim 13, wherein the angiogenic eye disorder is wet age-related macular degeneration.
15. The method of claim 14, wherein the VEGF receptor fusion protein is aflibercept.
16. The method of claim 13, wherein the angiogenic eye disorder is diabetic macular edema.
17. The method of claim 16, wherein the VEGF receptor fusion protein is aflibercept.

18. The method of claim 13, wherein the angiogenic eye disorder is diabetic retinopathy.
19. The method of claim 18, wherein the VEGF receptor fusion protein is aflibercept.
20. The method of claim 13, wherein the angiogenic eye disorder is non- proliferative diabetic retinopathy.
21. The method of claim 20, wherein the VEGF receptor fusion protein is aflibercept.
22. The method of claim 13, wherein the angiogenic eye disorder is proliferative diabetic retinopathy.
23. The method of claim 22, wherein the VEGF receptor fusion protein is aflibercept.
24. The method of claim 13, wherein the angiogenic eye disorder is macular edema following retinal vein occlusion.
25. The method of claim 24, wherein the VEGF receptor fusion protein is aflibercept.
26. The method of claim 13, wherein the VEGF receptor fusion protein is aflibercept.
27. The method of claim 1 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20° C.
28. The method of claim 27, wherein the angiogenic eye disorder is wet age-related macular degeneration.
29. The method of claim 27, wherein the angiogenic eye disorder is diabetic macular edema.

30. The method of claim 27, wherein the angiogenic eye disorder is diabetic retinopathy.

31. The method of claim 1 for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, in a volume of about 70 microliters, about 8 mg aflibercept; wherein the aflibercept is in an aqueous pharmaceutical formulation comprising about 114.3 mg/ml of the aflibercept and having a viscosity of about 5-15 cP at 20° C.

32. The method of claim 31, wherein the angiogenic eye disorder is wet age-related macular degeneration.

33. The method of claim 31, wherein the angiogenic eye disorder is diabetic macular edema.

34. The method of claim 31, wherein the angiogenic eye disorder is diabetic retinopathy.

35. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, about 70 microliters of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C.

36. The method of claim 35, wherein the angiogenic eye disorder is wet age-related macular degeneration.

37. The method of claim 35, wherein the angiogenic eye disorder is diabetic macular edema.

38. The method of claim 35, wherein the angiogenic eye disorder is diabetic retinopathy.

Ex.1001 at 61:50-64:40.

B. File History

39. The '036 patent derives from U.S. Patent Application No. 17/384,070 (the "'070 application"). The original claims of the '070 application recited "[a] method for treating an angiogenic eye disorder in a human patient in need thereof comprising administering an intravitreal injection of at least about 8 mg of a VEGF receptor fusion protein ... to the eye of the patient." Ex.2001 (Excerpted File History) at 2. The Examiner rejected those claims for not "provid[ing] adequate written description for the breadth of the formulation[s] encompassed by the claims." Ex.2001 at 231.

40. Regeneron amended the claims to recite a volume of about 100 microliters or less, a concentration of at least 100 mg/ml, and a viscosity of about 5-15 cP. Ex.2001 at 289. In support of the Amendment, Regeneron explained that "[i]ntravitreal injection of a liquid formulation into the eye should be done in a volume of about 100 microliters or less," as "[t]he vitreous chamber is a closed system having a typical volume of about 4-5 ml," such that introducing "excess volume into the eye risks damaging increases in intraocular pressure." Ex.2001 at 295. Regeneron further explained that "[i]n order to inject the target amount of VEGF receptor fusion protein (8 mg) in an acceptably low volume ($\leq$ 100 microliters), the concentration of the formulation must be relatively high, for example, greater than 100 mg/ml." Ex.2001 at 295.

41. Regeneron also asserted that the formulation must “have a viscosity suitable for injection via syringe,” as high-viscosity formulations “require excess pressure on the syringe plunger,” which may cause “damaging shearing forces to the protein and difficulty for the clinician who delivers the injection.” Ex.2001 at 295. “A major factor affecting [the] viscosity of VEGF receptor fusion protein formulations is protein concentration,” but “[l]owering protein concentration to lower viscosity” is not an option, because then “delivery of ≥ 8 mg of VEGF receptor fusion protein to the eye would need to be done in a higher volume,” risking “an increase in intraocular pressure if 100 microliters is exceeded.” Ex.2001 at 295-296. “In spite of being constrained by these factors”—*i.e.*, the difficulty associated with increasing protein concentration to achieve smaller injection volumes while avoiding increasing viscosity—the inventors “successfully developed several formulations that meet the[] criteria” recited by the claims. Ex.2001 at 296.

42. The Examiner accepted Regeneron’s amendment and arguments and allowed the patent to issue without further rejections, including on anticipation or obviousness grounds. The Examiner also did not issue any rejections based on the following references that Regeneron disclosed and the Examiner considered—Vitti (Ex.1007), Furfine (Ex.1005), Dix (Ex.1006), and Fiedler (Ex.1011). Alvotech relies on each of these references in its obviousness grounds, as well as Fiedler ’126 (Ex.2002), Australian Public Assessment Report for Aflibercept (Ex.2003,

“AusPAR”), Borwankar (Ex.2004), and Whitaker (Ex.2005). Ex.2001 at 236-37, 240, 251, 324, 371, 396-397, 400, 411, 527.

C. Priority Date

43. I am informed that the '036 patent claims priority on its face to the following provisional applications:

- U.S. Provisional Patent Application No. 62/813,882, filed March 5, 2019;
- U.S. Provisional Patent Application No. 62/769,876, filed November 20, 2018;
- U.S. Provisional Patent Application No. 62/752,127, filed October 29, 2018; and
- U.S. Provisional Patent Application No. 62/669,506, filed May 10, 2018.

44. I understand that Alvotech does not challenge whether the '036 patent is entitled to claim priority to the May 10, 2018, provisional filing date. *See, e.g.*, Pet. at 8 (“The earliest priority application was filed on May 10, 2018.”); Ex.1004 ¶ 28 (“For the purposes of my analysis of the '036 Patent, I have used the earliest priority date for the '036 Patent of May 10, 2018.”); Ex. 1004 ¶ 39 (similar).

V. The Person of Ordinary Skill in the Art

45. I have been informed that the disclosures of the '036 patent and the relevant prior art should be viewed from the perspective of a person of ordinary skill in the art (“POSA”) at the time of the claimed invention.

46. For the purpose of preparing this declaration in support of Patent Owner's Response, I have been asked to apply Dr. D'Amico's definition of a person of ordinary skill in the art. Under his definition, a POSA at the time of the invention would have been a multidisciplinary team that included (1) a medical doctor in ophthalmology or a similar field with knowledge of angiogenic eye disorders, including treatments and dosing regimens of drugs for intravitreal injection including anti-VEGF drugs, at least several years conducting research on anti-VEGF treatments for angiogenic eye disorders, and familiarity with the pharmacological properties of anti-VEGF treatments; and (2) a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture, and characterization of therapeutic proteins, including for example, fusion proteins or antibodies. Ex.1003 ¶ 90. I understand that under that definition, the POSA would have also had access to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs. Ex.1003 ¶ 90.

47. As an ophthalmologist with decades of knowledge and experience in treating angiogenic disorders, I have (and have had since at least May 2018) at least the skills and experience of part (1) of the POSA as defined by Dr. D'Amico. My

opinions in this report are expressed from the perspective of the clinician-POSA as of May 2018.

VI. Claim Construction

48. I understand that the words of a claim are generally given their ordinary and customary meaning, which is the meaning that the term would have to the person of ordinary skill in question at the time of the invention. I understand the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but also in the context of the entire patent.

49. I am informed that Alvotech's position is that no claim terms need construction. For the purpose of rendering my opinions, I apply the meaning that the claim terms would have to a POSA in question at the time of the invention of the '036 patent.

VII. The State of the Art As of May 2018

50. Below I provide a brief overview of the state of the art for the treatment of angiogenic eye disorders as of May 2018. Among other things, this section discusses the recognized need for long-acting anti-VEGF formulations that decrease injection frequency burdens on patients without sacrificing visual acuity outcomes or safety, and, along with the section that follows, shows that Regeneron succeeded in satisfying that demand despite the examples of unsuccessful efforts I have

described below. I reserve the right to offer additional opinions regarding the state of the art, or to expound on any opinions offered below, including in response to any additional evidence submitted by Alvotech.

A. VEGF and PlGF

51. Vascular Endothelial Growth Factors (“VEGF”) are a family of signaling proteins that serve as the principal regulators of blood and lymphatic vessel development. Ex.1037 at 3. The VEGF family includes placental growth factor (PlGF), VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E. Ex.1037 at 3. These VEGFs bind to receptors on target cells, such as vascular endothelial cells, that mediate angiogenic effects. Ex.1039 at 1178. Once VEGFs are bound to receptors, the cells are triggered to undergo angiogenesis, promoting the growth of new blood vessels from existing ones. Ex.1037 at 3.

52. While VEGF plays an important role in promoting new blood vessels from pre-existing vasculature—a process crucial for embryonic, postnatal development, and tissue repair—abnormalities in VEGF signaling can lead to various disease states stemming from the formation of leaky and abnormal vessels with poor perfusion. Ex.1037 at 10. Over-expression of these VEGF factors is known to play a central role in angiogenic eye disorders, with VEGF-A over-expression as the driving force. Ex.1037 at 11-12.

53. Aflibercept is a recombinant fusion protein consisting of the extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1. Ex.1041 at 89, 91. It functions as a soluble decoy receptor that binds to VEGF-A, VEGF-B, VEGF-C, and PlGF with higher affinity than their natural receptors, thereby inhibiting the binding and activation of those natural VEGF receptors. Ex.1041 at 91; Ex.1037 at 13. Aflibercept binds VEGF-A and PlGF dimers in a 1-to-1 ratio, a mechanism described as a “powerful ‘two-fisted grasp.’” Ex.1039 at 1179.

54. In contrast, other anti-VEGF agents, such as anti-VEGF monoclonal antibodies bevacizumab and ranibizumab, target only VEGF-A isoforms. Ex.1041 at 90; Ex.1029 at 375 (Table 1). Aflibercept also binds to VEGF-A with greater affinity than bevacizumab and ranibizumab. Ex.1029 at 375 (Fig 2). As a result, aflibercept more effectively prevents the activation of downstream receptors and the angiogenesis cascade. Ex.1041 at 91.

B. Angiogenic Eye Disorders

55. Angiogenic eye disorders due to overabundance of VEGF are a group of diseases characterized by the growth of abnormal blood vessels, often accompanied by growth of abnormal scar tissue in the eyes and vascular leakage from damaged pre-existing or new blood vessels, or both, all of which can and often do lead to severe vision loss. Ex.1037 at 3, 10-12.

56. Angiogenesis refers to the formation of new blood vessels from pre-existing vasculature and may be accompanied by growth of scar tissues. Ex.1037 at 3, 10. Wet Age-Related Macular Degeneration (“wAMD”) is an angiogenic eye disorder characterized by the growth of abnormal and fragile blood vessels, often with ingrowth of scar tissues when left untreated, which line the inner aspect of the back wall of the eye, and frequently involve the center of the retina called the macula. Ex.1041 at 90; Ex.1062 at xx-xxi. These fragile and abnormal vessels are prone to breaking and leaking fluid, damaging the macula or accompanying scarring of the retina. Ex.1062 at xxi. Because the macula forms the center of the retina essential for sharp vision, such accumulation of fluid or scarring can lead to visual impairment or vision loss of the part of the retina (the macula) used, for example, to read, drive, watch television, or recognize faces. Ex.1037 at 12.

57. Diabetic retinopathy is a complication of diabetes that affects the blood vessels within the inner aspect of the retina, closer to the center cavity of the eye. Ex.1019 at 1, 3. Diabetes can cause elevated sugar levels in the blood, leading to damage to the blood vessels that supply oxygen to the inner retinal cells. Ex.1022 at 2. When the inner retina is oxygen-deprived, cells up-regulate expression of VEGF. Ex.1022 at 2; Ex.1037 at 11. There are two stages of diabetic retinopathy, either of which may be accompanied by diabetic macular edema (or DME). Ex.1022

at 1. The two stages are termed non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Ex.1022 at 1.

58. Non-proliferative diabetic retinopathy includes closure of retinal capillaries that often may be recognized as dot and blot hemorrhages in the retina, or nerve fiber layer infarcts of the inner layer of the retina. Ex.1022 at 2, 4. As capillary closure becomes more severe, retinal abnormalities reflect this severe loss of capillary perfusion within the central and peri-central portion of the retina, including the macula, exhibiting extensive hemorrhages, beading of the retinal veins, or intraretinal microvascular abnormalities (IRMA)—a proliferation of new capillaries within the substance of the retina tissue. Ex.1022 at 1-2. These latter three signs are considered severe non-proliferative diabetic retinopathy, and eyes with severe NPDR have a higher chance of developing proliferative diabetic retinopathy and diabetic macular edema than eyes with NPDR without signs considered severe NPDR. Ex.1022 at 1-2; Ex.1019 at 2.

59. In the proliferative stage of diabetic retinopathy, the retina begins to form new blood vessels, a process called retinal neovascularization, on the surface of the retina. Ex.1022 at 1. These fragile blood vessels can cause bleeding into the vitreous, a jelly-like substance that fills the middle of the eye, causing patients to see dark floaters or lose central or peripheral vision or both. Ex.1022 at 3-5. If the bleeding worsens, it may block substantial parts of a patient's vision. Ex.1022 at 3-

5. In addition, these new blood vessels usually are accompanied by scar tissue, termed fibrous proliferans, which proliferate on the surface of the retina and often are intimately adherent to the outer aspect of the vitreous on the surface of the retina and the surface of the retina itself. This fibrous proliferation can contract and detach the retina off of the back wall of the eye, a process termed tractional retinal detachment. Ex.1022 at 4-5; Ex.1037 at 12. If the vitreous hemorrhage does not clear spontaneously or following the injection of anti-VEGF agents, patients may require surgical removal of the blood (a procedure called vitrectomy). Ex.1022 at 5. Tractional retinal detachments involving or threatening the center of the macula also may require surgical removal of the fibrous proliferans. Ex.1022 at 5.

60. VEGF also is a highly potent vascular permeability factor which can make existing retinal blood vessels leaky or hyperpermeable. Ex.1020 at 1382; Ex.1037 at 11. Subsequently, some patients with either non-proliferative or proliferative diabetic retinopathy also may develop a hyperpermeable condition due to over-expression of VEGF, called diabetic macular edema. Ex.1020 at 1375; Ex.1019 at 6. Diabetic macular edema refers to the accumulation of extracellular fluid in the macula leaking from existing inner retinal capillaries, which may be accompanied by lipid (lipoproteins within the fluid that may precipitate and become apparent as lipids, as the edema resorbs). Ex.1020 at 1375. While multiple hyperpermeable conditions driven by VEGF can cause macular edema, such as a

branch retinal vein occlusion, when the underlying cause of the macular edema is diabetes, the diagnosis becomes diabetic macular edema. Ex.1020 at 1375, 1378 (Figure 1); Ex.1037 at 12.

61. Diabetic macular edema is a vision-threatening complication of diabetic retinopathy and the most common form of vision impairment in individuals with diabetic retinopathy. Ex.1020 at 1375; Ex.1022 at 1. Diabetic macular edema, like poor perfusion or loss of perfusion of retinal capillaries from diabetes, also results from abnormal blood sugar levels causing damage to retinal capillaries with retinal production of VEGF that makes existing retinal capillaries become leaky and result in swelling or edema of the retina, frequently causing symptoms of central vision loss when occurring in the macula. Ex.1020 at 1375-76; Ex.1022 at 1-2. Diabetic macular edema may exist in the presence of non-proliferative or proliferative diabetic retinopathy. Ex.1022 at 1.

62. Macular edema following retinal vein occlusion (RVO) describes a specific type of macular edema caused by thrombus at the point of a retinal vein where a retinal artery and vein share an adventitial sheath that results in turbulent flow at this point, wherein blockage of the retinal venous system results in damage to the retinal capillaries and production of VEGF. Ex.1063 at 705-706; Ex.1064 at 70-71. RVO is classified into two main types depending on whether the thrombus occurs at the central retinal vein or a branch of the retinal vein: central retinal vein

occlusion (CRVO) and branch retinal vein occlusion (BRVO). Ex.1063 at 705. CRVO is characterized by blockage of the central retinal vein, affecting all four quadrants of the retina, and BRVO involves blockage of a branch of the central retinal vein, affecting the partial region of the retina drained by that branch retinal vein. Ex.1063 at 705. In both cases, the resulting macular edema, retinal capillary non-perfusion, or both, are the primary causes of vision loss associated with the condition, Ex.1064 at 70, but the consequences of an untreated BRVO tend to be less severe than an untreated CRVO on average, because unaffected portions of the retina with normal venous draining have no retinal damage. Ex.1063 at 705.

C. Intravitreal Injections

63. Intravitreal injection, also known as intravitreous injection, is a procedure in which a drug is injected directly into the vitreous cavity of the eye, which can result in delivery of the drug to the retinal tissues, while minimizing systemic absorption and exposure. Ex.1029 at 376-377, 379. In the United States, the procedure is typically performed in a clinical or outpatient setting under topical or local anesthesia. Ex.1014 at S3, S12-S14. After anesthetizing the surface of the conjunctiva at the site of the injection with anesthetic drops or gel, and sterilizing the ocular surface using povidone-iodine solution, an ophthalmologist inserts a fine-gauge needle—typically 30-gauge or slightly smaller—attached to a syringe with the drug, into the vitreous cavity to deliver the drug. Ex.1014 at S3, S4.

64. Although relatively uncommon—less than 1 in 5,000 injections—intravitreal injections can lead to endophthalmitis (a serious infection inside the eye) or retinal detachment (retina pulling away from its normal position due to a retinal tear developing in association with the intravitreal injection). Ex.2085 at 2; Ex.1014 at S5; Ex.1024 at 789. More commonly, perhaps in 1 in 100 injections, vitreous hemorrhage (bleeding inside the vitreous humor), or uveitis/iritis (inflammation of the uvea and iris, respectively), occurs due to a hypersensitivity reaction to the injected medication or its components. Ex.1014 at S5, S14; Ex.1024 at 788-789. Even more commonly, transiently elevated intraocular pressure (IOP) may occur due to increased volume from the injected drug, which may result in temporary or prolonged vision loss. Ex.1014 at S4, S11, S14. These complications can be observed following intravitreal administration of any drug, and all have been observed following intravitreal administration of anti-VEGF agents. Ex.1024 at 788-789.

65. Both volume and viscosity of the drug formulation are important factors affecting adverse events associated with intravitreal injections.

1. Viscosity

66. Intravitreal injections are ordinarily performed using a very fine needle, typically 30-gauge or finer. Ex.1014 at S13. Using a larger needle can increase the risk of complications, including vitreous hemorrhage, retinal damage, wound

leakage, and infection. Ex.1024 at 789-790; Ex.1015 at 4207. A larger needle puncture also can exacerbate patient discomfort. Ex.1014 at S13-14. For these reasons, the clinical standard in ophthalmology has consistently favored 30-gauge or finer needles for intravitreal injections. Ex.1014 at S13.

67. However, fine-gauge needles, such as 30-gauge needles or even smaller ones, can make delivery more difficult when a drug formulation is highly viscous because smaller inner-diameter needles require higher injection force. Ex.2115 at 352. In general, the narrower the needle, the more force is required to eject a drug from it. Ex.2115 at 352; Ex.2116 at 604. From a clinician's perspective, this means that a highly viscous intravitreal drug formulation can require greater finger pressure, make the plunger movement less smooth and predictable, increase injection time, and/or reduce the clinician's ability to deliver the dose in a controlled, steady manner while the needle is positioned in the eye. *See* Ex.2116 at 604; Ex.1010 ¶ 7. For the experienced ophthalmologist giving intravitreal injections, the ability to delicately control the injection matters because the patient is awake and aware that a needle is in the eye, and an uneven plunger movement or longer injection times can be a source of distress and anxiety.

68. High viscosity also creates a syringe-needle connection concern. When more force is needed to expel the drug, more pressure is transmitted through the syringe and needle assembly, including at the needle hub. Ex.2116 at 604, 608. This

pressure, in turn, may increase the risk of hub loosening, leakage, or even needle dislodgement. This risk is especially concerning when using a Luer slip syringe, where the needle is pushed onto the syringe tip and held by friction, as compared to a Luer lock syringe, which uses a threaded tip, requiring a needle or its attachment to be pushed and twisted into place, wherein the screw-on mechanism prevents the needle from popping off under pressure.

2. Volume and IOP

69. An increased volume of a drug also raises the potential risks associated with intravitreal injections because the vitreous cavity is a closed, fluid-filled compartment with limited capacity. *See* Ex.1029 at 376, Fig.3. Introducing extra fluid into the cavity transiently elevates IOP, and a larger injection volume can cause a more pronounced and sustained increase in IOP. Ex.1014 at S11. Acute increases in IOP have been observed in patients receiving as little as 0.05-mL intravitreal anti-VEGF injections, but are more common in volumes above 0.05-mL. Ex.2087 at 930-933.

70. Typically, after intravitreal injections, IOP returns to baseline within 30 minutes or less. Ex.2087 at 932-933. However, even transient IOP elevations can diminish capillary perfusion of the optic nerve—a structure transmitting all nerve signals from the retina to the brain. Ex.2123 at 808. A study conducted in 2007 studied short-term IOP changes after intravitreal injections of bevacizumab.

Ex.2123 at 807. While the study found that intravitreal injections are safe with respect to short-term changes, more than 10% of patients (13 out of 104 patients) experienced substantial, potentially clinically dangerous IOP spikes above 50 mm Hg. Ex.2123 at 809-810. The authors noted that such elevations could lower optic nerve head perfusion below autoregulatory levels and acutely deform the lamina cribrosa, which could be associated with subsequent irreversible damage to the optic nerve, though the long-term consequences remain unclear. Ex.2123 at 810.

71. Although IOP typically normalizes quickly, several studies have reported sustained (chronic) intraocular pressure elevations following intravitreal anti-VEGF injections (ranibizumab, bevacizumab, and pegaptanib) that persist beyond the initial 30–60 minutes. One retrospective study, Choi (Ex.2124), found that 9.4% (14 out 155 eyes) developed IOP above 25 mmHg, and 7 patients (5.5%) met the threshold for sustained elevated IOP beyond the date of injection—defined as IOP greater than 25 mm Hg on at least two separate visits or any elevation requiring glaucoma medication or surgery, in contrast to transient elevations within 30 minutes of the intraocular injection. Ex.2124 at 1028. A separate study, Tseng (Ex.2086), similarly reported sustained IOP elevation occurred in approximately 3.4% (19/555) to 4.5% (19/425) of patients treated with intravitreal anti-VEGF agents for neovascular AMD. Ex.2086 at 242. In that study, sustained IOP elevation was detected after a mean of 20 injections (range: 8–40), with the mean IOP at first

noted elevation reaching 29.8 mm Hg and the mean highest IOP reaching 35.8 mm Hg, compared with a baseline of 16.9 mm Hg. Ex.2086 at 242.

72. Of the eyes with sustained IOP elevation, the majority required IOP-lowering medications, and some required surgical intervention, both to try to reduce the risk of permanent optic nerve damage with visual field loss. Ex.2124 at 1028; Ex.2086 at 245. In the Choi study, of the nine eyes with elevated IOP, eight eyes required pressure lowering medications and one eye underwent a trabeculectomy. Ex.2124 at 1032-1033. In the Tseng study, 23 of 25 eyes required pharmacologic IOP reduction, and 6 eyes ultimately required laser trabeculoplasty or glaucoma filtration surgery. Ex.2086 at 245. Continued anti-VEGF treatment in the presence of sustained IOP elevation typically led to further IOP increases: in the Tseng study, all 19 affected eyes with sustained IOP elevation in which anti-VEGF treatment was continued eventually required some form of antiglaucoma intervention. Ex.2086 at 245.

73. Glaucoma patients may be particularly susceptible to damage from elevated IOP. Glaucoma refers to a group of conditions with an optic neuropathy, characteristic morphological changes in the optic nerve head and visual field defects. Ex.1015 at 4206. It is a leading cause of irreversible blindness worldwide, and one of the most common neuropathies. Ex.1015 at 4206. It is estimated that 60.5 million

people suffered from it in 2010 and that number is projected to increase to 111.8 million in 2040. Ex.1015 at 4206.

74. The primary goal in glaucoma management is to slow loss of optic nerve tissue, and one of the biggest risk factors for accelerated progression is an increased level of IOP. Ex.1015 at 4206. Lowering IOP remains the only proven therapy in everyday use. Ex.1015 at 4206. For this reason, patients with pre-existing glaucoma are at heightened risk of optic nerve damage from sustained IOP elevation following anti-VEGF injections. Ex.2086 at 245 (noting that the rate of sustained IOP elevations was 33% in eyes with preexisting glaucoma compared to only 3.1% in eyes without preexisting glaucoma). For glaucoma patients, even these transient elevations can cause permanent optic nerve damage and vision loss, and clinicians are particularly wary of any further IOP spikes that may be caused by subsequent and periodically-repeated intravitreal administration of anti-VEGF drugs. Ex.1014 at S3, S4, S7.

D. Clinical Studies of Anti-VEGF Agents Before Aflibercept

75. Eylea® (aflibercept 2 mg, in a 40 mg/ml formulation) was first approved by FDA in 2011. Before that time, clinicians had certain other intravitreal anti-VEGF agents available to them.

1. Macugen®

76. Macugen® (pegaptanib) is a synthetic RNA aptamer—*i.e.*, a short oligonucleotide with a molecular weight of 50 kD. Ex.1048 at 9. Macugen® was the first anti-VEGF medication to receive FDA approval for the treatment of wAMD in December 2004. Ex.1048 at 3-4. Pegaptanib selectively binds the VEGF-165, a VEGF-A isoform, with high affinity. Ex.1048 at 9; Ex.1047 at 6; Ex.1034 at 1-2. Pegaptanib does not block all isoforms of VEGF-A and is also unable to bind other members of the VEGF family, such as PlGF, VEGF-B, or VEGF-C. Ex.1048 at 7.

77. The clinical trials underlying Macugen®'s approval illustrate that increasing the dose of an anti-VEGF agent may *impede* clinical benefit while creating safety concerns. Notably, in the phase III V.I.S.I.O.N. trial, higher doses of pegaptanib failed to provide additional benefit and, in some cases, were associated with worse clinical outcomes. Exs.2088 at 2805, 2809-2811.

78. In the V.I.S.I.O.N. study, participants with AMD were randomized to receive intravitreal injections of pegaptanib at 0.3 mg, 1.0 mg, 3.0 mg, or a sham injection, every six weeks over 48 weeks (totaling nine doses). Ex.2088 at 2805. When the results were analyzed for the subgroup of patients evaluated both at baseline and week 54—thereby minimizing the impact of missing data—0.3 mg pegaptanib was plainly superior to sham treatment, but there was no definitive evidence that 3.0 mg pegaptanib was superior to sham treatment. Ex.2088 at 2810.

79. Specifically, at week 54, a loss of fewer than 15 letters was observed in 192 (71%) of 271 participants assigned to 0.3 mg ($P < .001$), 198 (72%) of 275 participants assigned to 1.0 mg, and 166 (63%) of 264 participants assigned to 3.0 mg of pegaptanib ($P = .14$), compared with 154 (56%) of 275 participants assigned to sham injection. Ex.2088 at 2805, 2808-2809. The risk of severe vision loss (30 or more letters) was 22% in the sham injection group, and among the treatment groups, the risk of severe vision loss was highest in the 3.0 mg group (14%) compared with the 0.3 mg group (10%) and 1.0 mg group (8%). Ex.2088 at 2809-2810.

80. A separate safety-pharmacokinetic trial further investigated higher doses of pegaptanib and confirmed that increasing the doses above 0.3 mg did not improve efficacy but did increase adverse effects. Ex.2103 at 1707-1708. All 0.09-mL injections of all three doses—0.3 mg, 1 mg or 3 mg—were associated with elevated IOP: on average, IOP measured 3 to 8 mmHg higher 30 minutes after injection compared to baseline, with the largest increases observed in the 3 mg group. Ex.2103 at 1708. Notably, IOP elevations to 35 mmHg or higher—a monitoring threshold suggested by the Independent Data Monitoring Committee—were observed in 2 of 54 participants (4%) receiving 1.0 mg, and 12 of 56 participants (21%) receiving 3 mg in the randomized cohorts; and 7 of 37 participants (19%) receiving 3 mg in the open label cohort. Ex.2103 at 1708,

1712.e2 & Table 5. At these levels, there is risk of glaucomatous damage, and in patients with pre-existing optic nerve damage from glaucoma or other conditions, severe vision loss may occur. Ex.2085 at 3. In addition, three participants in the 3.0 mg group required a single post-injection paracentesis—a minimal, but invasive, precise eye procedure done to rapidly lower the IOP, in which an ophthalmologist creates a tiny, controlled incision at the edge of the cornea to access and drain a small amount of fluid (aqueous humor) from the front part of the eye. Ex.2103 at 1708. These IOP differences between doses cannot be attributed to volume because all three doses were delivered at the same volume of 0.09 mL. Ex.2103 at 1703.

81. The combination of these findings likely contributed to the selection of a lower dose, 0.3 mg, as the approved clinical dose, as it offered the best balance of efficacy and safety: the 0.3 mg dose was no less efficacious than the 1.0 mg dose and likely more efficacious than 3.0 mg dose. Ex.1048 at 2.

82. Although Macugen® demonstrated statistically significant and clinically meaningful benefits for patients with neovascular AMD, it was rapidly overtaken in clinical practice by more effective and safer monoclonal antibodies ranibizumab (Lucentis®) and bevacizumab (Avastin®). Ex.1034 at 2141-2142; Ex.1039 at 1181; Ex.1047 at S4.

2. Bevacizumab

83. Bevacizumab, commercially known as Avastin®, is a full-length, humanized murine monoclonal IgG1 antibody with a molecular weight of 149 kDa. Ex.1011 at [0075]. Bevacizumab inhibits angiogenesis by binding and neutralizing all isoforms of VEGF-A, thereby preventing VEGF from interacting with its receptors (VEGFR1 and VEGFR2) on endothelial cells. Ex.1029 at 375. However, it does not bind to other VEGF family members, such as PlGF, VEGF-B, or VEGF-C. Ex.1029 at 375. Bevacizumab can simultaneously bind to two VEGF dimers (a 1:2 bevacizumab-to-VEGF dimer ratio). Ex.1039 at 1179. According to its label, bevacizumab has an estimated half-life of 20 days (ranging from 11 to 50 days), Ex.2104 at 22, but the estimated intravitreal half-life is approximately 9.82 days . Ex.2108 at 1847.

84. Bevacizumab was the first anti-VEGF agent approved by the FDA. Ex.1037 at 1, initially for the treatment of metastatic colorectal cancer in 2004. Ex.2104 at 1, 22; Ex.2106 at 102-103. Since then, it has gained FDA approval for multiple cancer indications, including first-line advanced non-squamous non-small cell lung cancer, metastatic renal cell carcinoma, and recurrent glioblastoma. Ex.2104 at 3-4, 26-28. However, it is not FDA-approved for any ophthalmic indications. *See* Ex.2104 at 2-4.

85. Despite being approved only for the treatment of cancer, bevacizumab has been widely used off-label for the treatment of neovascular (wet) AMD, diabetic macular edema, and retinal vein occlusion. Ex.1037 at 14. Although originally intended for intravenous administration, bevacizumab is administered via intravitreal injection for ophthalmic purposes. Ex.1029 at 374. Off-label ophthalmic use began around 2005, Ex.1039 at 1176, driven by its similar VEGF-A specificity to ranibizumab and its much lower cost (\$15–50 per injection for bevacizumab versus approximately \$2,000 per injection for ranibizumab). Ex.1041 at 95.

86. The landmark CATT (Comparison of Age-Related Macular Degeneration Treatment Trials) study demonstrated non-inferiority between monthly bevacizumab and monthly ranibizumab, with vision gains of +8.0 versus +8.5 letters, respectively. Ex.1017 at 1897; Ex.1039 at 1182. Due to its cost-effectiveness and efficacy, bevacizumab has been widely used for intravitreal treatment of angiogenic eye disorders off label. Ex.1037 at 12, 14; Ex.1015 at 4206.

3. Ranibizumab

a. FDA-Approved Product and Registration Trials

87. Ranibizumab, commercially known as Lucentis®, is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment without the Fc region of the full antibody designed specifically for intraocular use. Ex.1055 at 14. Ranibizumab has a molecular weight of 48 kDa and is much smaller than its parent

molecule bevacizumab (149 kDa) and aflibercept (115 kDa). Ranibizumab blocks all isoforms of VEGF-A isoforms, but does not bind to other VEGF family members, such as PlGF, VEGF-B, or VEGF-C. Ex.1029 at 375 (Table 1). Two ranibizumab molecules can bind to one VEGF dimer (a 2:1 ratio of ranibizumab to VEGF dimer). Ex.1029 at 375 (Figure 2).

88. The estimated average vitreous elimination half-life of ranibizumab is approximately 9 days, based on a population pharmacokinetic analysis of patients with neovascular AMD using serum disappearance data. Ex.1055 at 16; Ex.2108 at 1848. In primates, the intravitreal half-life of ranibizumab is approximately 3 days. Ex.2108 at 1848. The aqueous half-life of intravitreal ranibizumab 0.5 mg is 7.19 days in human eyes. Ex.2108 at 1848. Because ranibizumab lacks the Fc portion found in full-length antibodies, it has a reduced serum half-life, which may limit systemic exposure and thus systemic toxicity. Ex.2108 at 1848.

89. In June 2006, ranibizumab received FDA approval for the treatment of wet age-related macular degeneration (wAMD), following positive results from two phase III clinical trials: the MARINA and ANCHOR studies. Ex.1062 at xxii. In the MARINA trial, 95% and 96% of participants in the 0.3 mg and 0.5 mg ranibizumab treated groups lost fewer than 15 letters of best-corrected visual acuity (BCVA) on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, compared with just 62% in the sham injection group. Ex.1062 at xxii. The treatment

effects of ranibizumab were similar to those observed in the MARINA trial despite the presence of active control, verteporfin photodynamic therapy (PDT) group, because the ANCHOR trial included patients with wAMD lesions with a fluorescein angiography pattern (predominantly classic) that responds better to PDT than no treatment. Ex.1062 at xxii. Together, MARINA and ANCHOR established monthly ranibizumab injections as the standard treatment for wAMD. Ex.1058 at 78.

90. The recommended dose of ranibizumab for the treatment of neovascular AMD is 0.5 mg (0.05 mL of 10 mg/mL solution) administered by intravitreal injection once a month (approximately every 28 days). Ex.1055 at 1. Since its initial approval, ranibizumab has also received FDA approval for the treatment of macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy in patients with DME, and myopic choroidal neovascularization (mCNV). Ex.1055 at 1.

b. The HARBOR Trial

91. After ranibizumab was approved at the 0.5 mg dose, Genentech undertook a study (HARBOR) to determine whether increasing the dose to 2 mg would provide clinical benefits. The study concluded the increased dose would *not* provide clinical benefits to patients, and Genentech did not pursue a higher-dose product. Ex.1055 at 1 (the highest dose as indicated on the label remains at 0.5 mg). This is just one of many examples in the prior art of companies trying, but failing,

to achieve a “better” clinical result (whether in terms of efficacy or duration of effect) by increasing the dose of an anti-VEGF agent.

92. The HARBOR trial was a phase III study designed to evaluate the efficacy and safety of ranibizumab in patients randomly assigned to receive either 0.5 mg or 2.0 mg doses. Ex.1026 at 2182. During the initial loading phase, all patients received three consecutive monthly intravitreal injections of ranibizumab (0.5 mg or 2.0 mg). Ex.1026 at 2183. Afterwards, the participants were further randomized to receive injections either monthly or on an as needed basis (“PRN”). Ex.1026 at 2183. The participants in the PRN groups were evaluated monthly and re-treated only if clinical assessment by a designated physician (masked) indicated a need for retreatment. Ex.1026 at 2183. If retreatment was not indicated, the treating physician (unmasked) administered a sham injection. Ex.1026 at 2183. Retreatment criteria included a decrease in visual acuity of five or more letters from the previous visit, or evidence of VEGF activity on OCT (such as subretinal fluid or intraretinal fluid). Ex.1026 at 2183. All four groups were monitored monthly for 24 months. Ex.1026 at 2181. The aim was to assess whether a higher dose or PRN dosing or both provided additional benefits compared with the established 0.5 mg monthly regimen. Ex.1026 at 2182.

93. Its results were published in two papers—Busbee (Ex.2110) and Ho 2014 (Ex.1026). Busbee was the initial peer-reviewed publication reporting the

primary outcome of the HARBOR trial, whereas Ho presented additional trial results based on post hoc descriptive statistics. Dr. D’Amico evidently did not consider the Busbee publication in forming his opinion. Although Dr. D’Amico apparently did consider the Ho publication, he does not reference it when discussing the HARBOR results. Instead, he relies on Stewart (Ex.1039), a narrative review—subject to greater bias in interpretation of the results compared with a systematic review with meta-analyses—published one year before Busbee and two years before Ho. For its underlying data, Stewart relies on “Data on file, Genentech [a study sponsor]”—data not yet available in any published peer-reviewed, primary outcome publications. Ex. 1039 at 1182.

94. In my opinion, the POSA seeking to interpret the results of HARBOR would have first looked to Busbee and Ho, containing the standardized reporting of a randomized clinical trial including associated statistical analyses, rather than a narrative review published two years earlier. Indeed, I note Dr. D’Amico appeared to have a similar instinct, when he testified at deposition to his belief that the Stewart review was published *after* the Ho paper, but then realized at his deposition that Stewart was published *before* Ho and the other study investigators published their results. Ex.2053 at 244:21-246:12.

95. In my opinion, a POSA reading Stewart’s speculation—published without access to the primary outcome paper or independent peer review—that the

HARBOR trial in combination with the VIEW trials (which I address below and for which Dr. D’Amico likewise did not consider the primary publications), “suggest[s], but do[es] not prove, that increasing the dose of a drug prolongs its duration of action (durability),” Ex.1039 at 1182, would have discounted that statement. This is particularly true given that, two years later, the HARBOR study investigators concluded the opposite: “[o]ver 2 years, the 2.0 mg dose did not show any clinically meaningful difference in efficacy, *durability*, or safety compared with the 0.5 mg ranibizumab dose.” Ex.1026 at 2190 (emphasis added).

**1) The One Year HARBOR Results
(Ex.2110) Do Not Support A Clinical
Benefit for Increased Ranibizumab Doses**

96. A key finding of the HARBOR trial was that increasing the ranibizumab dose to 2.0 mg—a four-fold increase over the FDA-approved dose of 0.5 mg—did not provide additional visual acuity benefits or superior clinical outcomes compared with the approved 0.5 mg dose at the one-year primary outcome endpoint. Ex.1026 at 2190. At month 12, the 2.0 mg monthly group did not meet the pre-specified superiority criteria, and both 0.5 mg and 2.0 mg PRN groups failed to meet the non-inferiority margin. Ex.2110 at 1046.

97. Specifically, at month 12, the 2.0 mg monthly group gained 9.2 letters from baseline, compared with 10.1 letters from baseline for the 0.5 mg group, resulting in a mean difference of 0.9 letters (95% confidence interval (“CI”): -3.4 to

1.3 letters). Ex.2110 at 1049-1050. This difference showed that the visual outcome of the 2.0 mg dose was not statistically significantly superior, and certainly not superior to a clinically relevant degree, compared with the visual acuity outcomes of the 0.5 mg group. Ex.2110 at 1053.

98. The non-inferiority comparisons between PRN and monthly dosing likewise failed, indicating that PRN dosing of the higher dose ranibizumab may lead to worse visual outcomes than monthly dosing. Ex.2110 at 1053. The non-inferiority margin refers to a pre-specified threshold in a clinical trial that defines how much worse a new treatment can be compared to an existing standard treatment, while still being considered clinically acceptable. For this study, the pre-specified non-inferiority margin was 4 letters, meaning that if the lower boundary of the confidence interval crossed beyond 4 letters, the comparison would fail to demonstrate non-inferiority. Ex.2110 at 1049.

99. At month 12, the comparison between 0.5 mg PRN and 0.5 mg monthly dosing showed a mean difference of -2.0 letters (97.5% CI: -4.5 to 0.6 letters), while the comparison between 2.0 mg PRN and 0.5 mg monthly dosing showed a mean difference of -1.6 letters (98.4% CI: -4.4 to 1.1 letters). Ex.2110 at 1049. Because the confidence interval boundaries crossed -4 letters margin in both PRN-versus-monthly comparisons, both 0.5 mg PRN and 2.0 mg PRN failed to clear the non-inferiority threshold for visual acuity. All pre-specified secondary visual acuity

outcomes (such as anatomical differences) at month 12 likewise showed no superiority of 2.0 mg monthly over 0.5 mg monthly, and no superiority of 2.0 mg PRN over 0.5 mg monthly. Ex.2110 at 1050-1051. These results indicated that longer intervals between treatments potentially sacrificed visual acuity irrespective of increased dose—the outcomes with PRN dosing were either worse than monthly dosing at either dose level, or at best no different and not demonstrably superior.

100. The mean number of injections over the course of the year was 7.7 for the 0.5 mg PRN group and 6.9 for the 2.0 mg PRN group, a difference of only 0.8 injections over 12 months. Ex.2110 at 1046. Such a small difference, under 1 injection, would also have shown a POSA that the duration of a PRN dose at 2.0 mg was not shown to be meaningfully different from the duration of the PRN dose at 0.5 mg.

2) The Two-Year HARBOR Results (Ex.1026) Do Not Support a Clinical Benefit for Increasing Ranibizumab Dose

101. Results at two years were similar to the outcomes at one year, though no formal statistical comparisons were provided for the two-year outcomes as the study was not powered to compare efficacy outcomes between the treatment groups at that time point. The magnitude of the point estimate differences for efficacy at 24 months between monthly 0.5 mg compared with monthly 2.0 mg, and PRN 0.5 mg compared with PRN 2.0 mg ranibizumab were similar to the month 12 results. The

results at month 24 showed that mean BCVA gains were +9.1 letters (0.5 mg monthly) versus +8.0 letters (2.0 mg monthly), and +7.9 letters (0.5 mg PRN) versus +7.6 letters (2.0 mg PRN). Ex.1026 at 2182, 2188. This would have indicated to the POSA that the higher dose did not confer clinical superiority. The POSA would have understood that the visual acuity outcomes either were worse with PRN compared with monthly at either dose, or at best were no different but not superior. Specifically, the average improvement from baseline in visual acuity was a gain of 9.1 letters for monthly 0.5 mg group vs 8.0 letters for the 2.0 mg PRN group, wherein the 1.1 letter deficit for the 2.0 mg PRN, even without a model-adjusted mean difference, confidently would fail the non-inferiority margin of 4 letters. Ex.1026 at 2182.

102. The average gain from baseline for 0.5 mg PRN of 7.9 letters compared with 7.6 letters in the 2.0 mg PRN group, again favoring the 0.5 mg PRN group by 0.3 letters, even without a model-adjusted mean difference, confidently would fail the non-inferiority margin of 4 letters. Ex.1026 at 2184-2185. The proportion of patients achieving 15 or more letters of improvement at month 24 was not different between the two doses: 34.5% and 37.6% in the 0.5 mg and 2.0 mg monthly groups, and 33.1% and 34.8% in the 0.5 mg and 2.0 mg PRN groups, respectively. Ex.1026 at 2185. All other visual acuity outcomes at month 24 showed no confident superiority of 2.0 mg monthly compared with 0.5 mg monthly, and no superiority of

2.0 mg PRN compared with 0.5 mg monthly. Ex.1026 at 2184. Thus, the POSA would have understood that quadrupling the clinical dose of ranibizumab failed non-inferiority—that is, the POSA would have understood that increasing to a 2.0 mg dose might sacrifice visual acuity outcomes compared with a 0.5 mg dose.

103. The POSA also would have understood that the duration of the PRN dose at 2.0 mg was not shown to be meaningfully different from the duration of the PRN dose at 0.5 mg. During Year 2 of the study, the 0.5 mg PRN group had a mean of 5.6 injections compared with a mean of 4.3 injections for the 2.0 mg group, which is a difference of only 1.3 injections over 12 months. Ex.1026 at 2185, 2188. Nevertheless, the POSA reading the HARBOR results would understand that a 95% confidence interval would likely dip below 1.0 injections over the course of twelve months.¹ Said differently, the POSA could not have reasonably expected, based on these data, that quadrupling the dose of ranibizumab would save his or her patients, on average, at least a single injection over the course of a year.

104. The POSA would have reached a similar conclusion when comparing the difference in the mean number of injections over 2 years in the PRN groups—i.e., 13.3 for 0.5 mg PRN and 11.2 for 2.0 mg PRN, equating to a point estimate difference over two years of 2.1 injections. Ex.1026 at 2185, 2188. Nevertheless,

¹ In my opinion, this actually overestimates the confidence the POSA would have in these point estimates data, given the need to control for multiple analyses in Year 2.

the POSA reading the HARBOR results would understand that a 95% confidence interval around the point estimate difference of 2.1 injections would likely dip below 2.0 injections over the course of twenty-four months. In other words, the POSA would have reasonably believed, based on these data, that quadrupling the dose of ranibizumab would likely save his or her patients fewer than two injections over the course of two years. Consistent with my opinion, the authors of the HARBOR study concluded that the “2.0 mg dose did not show any clinically meaningful difference in efficacy, durability, or safety compared with the 0.5 mg ranibizumab dose.” Ex.1026 at 2190. Genentech, sponsor of the HARBOR study, also understood the results of the HARBOR study to mean that “[h]igher molar doses of anti-VEGF do not lead to greater efficacy or durability.” Ex.2126² at 22. I agree with their conclusion.

105. Thus, the POSA would have understood from the HARBOR results that quadrupling the FDA-approved dose of ranibizumab to 2.0 mg produced visual acuity outcomes that were certainly not superior (and in fact were possibly *inferior*) to those achieved by the normal 0.5 mg dose. And the POSA would have understood from the HARBOR results that quadrupling the FDA-approved dose of ranibizumab

² I note that this slide was presented and became publicly available on February 16, 2021, after the priority date. However, I am informed by counsel that such later failures of others could serve as objective evidence supporting non-obviousness.

to 2.0 mg did not impart any clinically meaningful improvement in duration of effect or reduction in injection burden for patients. In short, HARBOR would have taught the POSA that there was no clinical benefit to increasing ranibizumab dosing.

106. Thus, if the POSA believed that these ranibizumab results could be extrapolated to the class of anti-VEGF agents (i.e., including aflibercept) as Dr. D’Amico suggests (Ex.2053 at 413:17-22), the POSA reading HARBOR would have understood that there was no clinical benefit to increasing the dose of an anti-VEGF agent.

E. Clinical Studies of Aflibercept (Eylea® 2mg)

107. Aflibercept (currently sold as Eylea®) 2mg is an anti-VEGF drug, first approved by the FDA for treating wAMD in November 2011. Ex.1050 at 15. Regeneron’s Eylea® product contains 40 mg/ml of aflibercept (among other ingredients) in a 50 microliter volume, yielding a 2 mg dose. Ex.1050 at 1.

1. Pre-clinical Animal Studies

108. Before human clinical trials, a study sponsor conducts pre-clinical animal studies to evaluate pharmacology, pharmacokinetics and toxicology. Ex.1058 at 23. For Eylea®, studies were conducted in vitro and in mice, rats, rabbits, and monkeys and deemed adequate to support clinical intravitreal (IVT) treatment. Ex.1058 at 23.

109. The toxicity studies consisted of single-dose studies in rats and ocular repeat-dose toxicity studies in monkeys. Single doses were administered by intravenous administration (at doses of 50, 150, and 500 mg/kg) to rats. Ex.1058 at 19. Transient skin lesions and discoloration of the tail were observed at 150 mg/kg. Ex.1058 at 19. Repeat-dose toxicity studies were conducted in Cynomolgus monkeys, with IVT injections up to 13 weeks (sub-chronic) and up to 8 months (chronic). Ex.1058 at 20.

110. Following IVT administrations, inflammatory responses in the anterior chamber of the eye were observed but did not appear to be dose- or treatment duration-dependent. Ex.1058 at 20. Increased intraocular pressure was also noted in injected eyes, likely due to the increased vitreal volume (50 µl/eye) from the intravitreal injection. Ex.1058 at 20. With findings of adverse events at 2 mg and 4 mg/eye levels, a NOAEL (No-Observed-Adverse-Effect Level) was established at 500 µg/eye, and a LOAEL (Lowest-Observed-Adverse-Effect Level) at 2 mg/eye. Ex.1058 at 20. The NOAEL represents the “highest dose level that does not produce a significant increase in adverse effects in comparison to the control group,” while LOAEL is the lowest tested dose in an animal species with adverse effects. Ex.2109 at 5, 15.

111. Systemic repeat-dose toxicity studies were conducted in mice, rats and Cynomolgus monkeys via intravenous administration at a much higher

concentration compared to IVT administration. Ex.1058 at 20. The negative effects were observed in various organs, including bone, kidneys, adrenals, ovary and nasal cavity. Ex.1058 at 20. No NOAEL could be determined in these studies because of the effects on target organs and microscopic findings, which included vascular alterations, vascular degeneration and fibrosis in multiple tissues including the heart, and hepatic portal inflammation and necrosis. Ex.1058 at 20.

2. CLEAR-IT 1

112. The Phase I CLEAR-IT 1 (Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial) evaluated the safety and efficacy of intravitreal aflibercept. Ex.1034 at 2141; Ex.1039 at 1180; Ex.1041 at 92. A total of 21 participants received a single dose of aflibercept ranging from 0.05 mg to 4 mg. Ex.1034 at 2141. In this study, the results for the six participants who received either 2 or 4 mg of aflibercept showed 13.5 letters of improvement in visual acuity, accompanied by reductions in excess foveal thickness. Ex. 1034 at 2141. However, the study did not report baseline visual acuity for those participants or the results that distinguish between the 2 mg and 4 mg groups. Ex.1034 at 2145-2146.

3. CLEAR-IT 2

113. The Phase II CLEAR-IT 2 study was designed to further investigate the optimal dose and dosing frequency by randomly assigning patients to varying doses and dosing schedules. Ex.2089 at 1090. A total of 159 participants were randomized

into five groups: 0.5 mg or 2 mg administered every 4 weeks (monthly dosing on day 1 and at weeks 4, 8, and 12), or 0.5 mg, 2 mg, or 4 mg administered every 12 weeks (quarterly dosing on day 1 and at week 12). Ex.2089 at 1090.

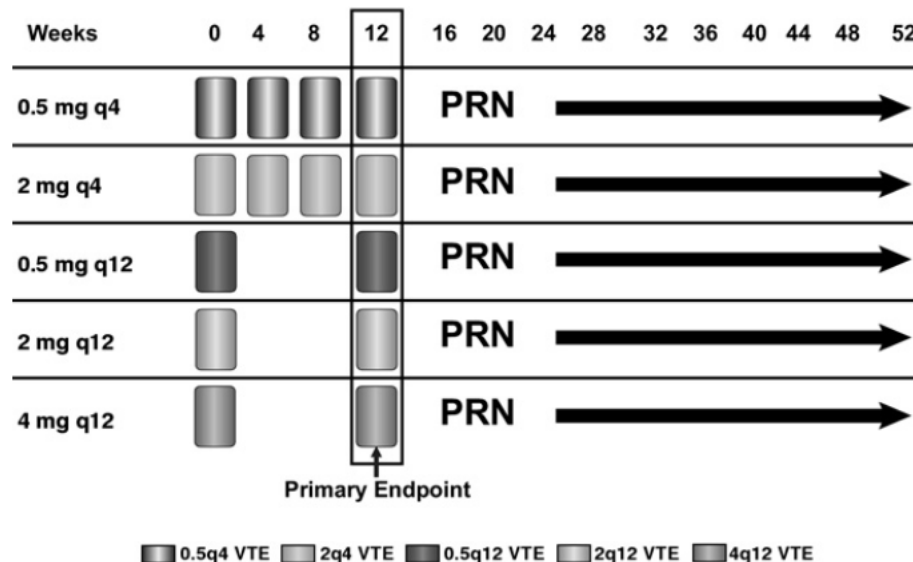
114. After week 12, all groups were retreated PRN with their originally assigned dose and were evaluated monthly. Ex.2118 at 1098. PRN dosing was given if any of the following criteria were met: an increase in central retinal/lesion thickness (CR/LT) by at least 100 microns; a loss of at least 15 letters in visual acuity accompanied by recurrent or persistent fluid on optical coherence tomography (OCT); new-onset classic choroidal neovascularization on fluorescein angiography; new or persistent fluorescein leakage on fluorescein angiography; or new macular hemorrhage. Ex.2118 at 1100.

115. At week 12, all dosing groups showed a statistically significant mean improvement in visual acuity compared with the baseline visual acuity as measured by the best-corrected visual acuity letter score on an ETDRS chart. Ex.2089 at 1092-1093. Notably, among study arms, patients in the 4 mg quarterly group demonstrated the smallest gains in visual acuity at the primary endpoint of twelve weeks—patients receiving 0.5 mg or 2 mg quarterly experienced better visual acuity outcomes at this timepoint, as did patients receiving monthly doses of 0.5 mg or 2.0 mg. Ex.2089 at 1093-1094; Figs. 3, 4, 5. Data from week 16 confirmed this trend: monthly dosing groups outperformed all quarterly dosing groups, and out of the 0.5

mg, 2 mg and 4 mg quarterly groups, the patients receiving the 4 mg dose showed the least visual acuity improvements. Thus, the results did not suggest that increasing the dose to 4 mg would provide better efficacy or longer duration of effect.

116. With respect to central retinal thickness, treatment with aflibercept led to significant decreases across all dosing groups compared with baseline thickness. Ex.2089 at 1092. At twelve weeks, the mean reductions in the monthly groups were 153.5 μm for the 0.5 mg, 169.2 μm for the 2 mg group; in the quarterly groups, the mean reductions were 75.6 μm for 0.5 mg, 56.3 μm for 2 mg, and 139.8 μm for 4 mg. Ex.2089 at 1093 (Fig. 2). Monthly dosing at 0.5 and 2 mg produced statistically greater mean reductions than any quarterly regimen. Ex.2089 at 1092. Put differently, both the 0.5 mg and 2 mg monthly groups outperformed the quarterly 4 mg arm, meaning that an increase in dose to 4 mg quarterly did not lead to anatomical improvements. Ex.2089 at 1092.

117. After the primary endpoint at week twelve, participants in the CLEAR-IT 2 study entered a PRN dosing phase, as reflected in Figure 2 of Heier 2011 (Ex.2118), which reports the one-year results of CLEAR-IT 2. Again, for reasons I do not understand, Dr. D'Amico did not consider this publication either.



Ex.2118 at 1100 (Figure 2).

118. During the PRN phase that took place from week 16 to 52, participants received 0.5, 2, or 4 mg of aflibercept as needed. Ex.2118 at 1099. Participants who had received 0.5 mg monthly or quarterly for the first twelve weeks received 0.5 mg as needed between weeks 16 and 52. Ex.2118 at 1100. Participants who received 2 mg monthly or quarterly for the first twelve weeks received 2 mg as needed between weeks 16 and 52. Ex.2118 at 1100.

119. Overall, PRN dosing at weeks 16 through 52 maintained the significant anatomic and vision improvements compared with baseline established during the 12-week fixed-dosing phase. Ex.2118 at 1098. The most robust improvements and consistent maintenance of visual acuity were generally observed in patients who initially received 2 mg monthly dose. Ex.2118 at 1098.

120. Although participants receiving 4 mg aflibercept during the PRN phase did have reduction in central retinal thickness on par with patients who initially received monthly 2 mg doses, the same was not true of visual acuity. Ex.2118 at 1098 (Fig. 5). From week 12 to 52, participants who received 4 mg aflibercept consistently had worse visual acuity than participants who received initial monthly doses of 0.5 mg or 2 mg aflibercept. Ex.2118 at 1098 (Fig. 5). In fact, even patients receiving 0.5 mg during the PRN phase experienced better gains in visual acuity than those receiving 4 mg—so long as those patients had received *monthly* doses of 0.5 mg in the fixed-dosing stage. Ex.2118 at 1098 (Fig. 5). The POSA would have concluded from these data that more frequent dosing of aflibercept is needed irrespective of dose, not that a larger dose works better or lasts longer.

121. The reinjection outcomes reported in the PRN phase of CLEAR-IT 2 likewise would have suggested to the POSA that increasing dose does not increase duration of effect. Below, I have highlighted Table 4 from Heier 2011 (Ex.2118) to show participants receiving 0.5 mg aflibercept as-needed during weeks 12-52 in yellow, participants receiving 2 mg aflibercept as-needed during weeks 12-52 in blue, and participants receiving 4 mg aflibercept as-needed during weeks 12-52 in red.

Table 4. Retreatment Outcomes with VEGF Trap-Eye

Treatment Regimen	Mean No. of Injections over PRN Phase (Weeks 12–52)	Mean No. of Days to First Injection over PRN Phase (Weeks 12–52)	Median No. of Days to First Injection over PRN Phase (Months 3–12)
0.5 mg q4	2.52	102	85
2 mg q4	1.55	160	150
0.5 mg q12	1.84	133	86
2 mg q12	2.48	113	86
4 mg q12	1.7	138	111
All groups	2.01	129	110

PRN = as-needed.

122. As is evident, the results of the PRN phase do not demonstrate that dosing patients with 4 mg quarterly results in a longer duration of effect than dosing patients with 2 mg monthly. Instead, to the extent duration of effect can be estimated using the number of injections participants received during weeks 12-52 and number of days after week 12 they required their first injection, the POSA would have concluded that there was little if any difference in dose duration observed among the treatment arms over the course of nine months. Even if the POSA took the point estimates provided in Table 4 at face value (without supplied confidence intervals around the pairwise comparison differences), the POSA would have concluded that there was no reliable relationship between dose and duration of effect.

123. For example, if the POSA first compared results for only participants who were in a quarterly-dosing arm during weeks 12-52, the POSA would see that participants receiving the lowest dose (0.5 mg) of aflibercept needed 0.64 *fewer* injections and lasted, on average, 20 days *longer* before requiring their first “as-

needed” injection after week 12 than did participants receiving the 2 mg aflibercept dose. Participants receiving 4 mg aflibercept required only *0.14* fewer injections over the course of nine months than did patients receiving 0.5 mg aflibercept, and on average lasted only five days longer before requiring their first re-injection after week 12. The inconsistency in dose response and the small reported differences between these study arms would suggest to the POSA that increasing the dose of aflibercept would not be expected to produce a reliable or clinically meaningful difference in duration.

124. Likewise, the POSA considering whether to pursue a high-dose aflibercept product would have compared the PRN-phase results of study participants in the 4 mg quarterly arm to the 2 mg *monthly* arm. During the PRN phase, participants in the 2 mg monthly arm were subject to the same treatment regimen as participants in the 2 mg quarterly arm—both sets of participants received a dose of 2 mg at week twelve and then doses of 2 mg thereafter as needed. As Table 4 reflects, patients who received a 4 mg dose of aflibercept at week 12 needed 0.15 *more* injections than patients who received a 2 mg dose of aflibercept at week 12, provided those patients had received monthly aflibercept previously. And patients who received a 4 mg dose of aflibercept at week 12 needed injections on average about 23 days *sooner* than patients who received a 2 mg dose of aflibercept at week 12, provided those patients had received monthly aflibercept previously.

125. Thus, from Brown and Heier 2011, the POSA would have understood that there was no reason to expect that increasing the dose of aflibercept above the 2 mg would provide additional clinical benefit, either in terms of efficacy or duration of treatment. In addition, a POSA would have had no evidence that increasing the dose beyond 2 mg—for example, to 4 and 8 mg—would be likely to improve visual acuity or provide greater durability to allow longer intervals between injections without compromising visual outcomes. This would have further dissuaded from selecting doses higher than 2 or 4 mg, such as 6 mg or 8 mg doses.

126. The Stewart review article (Ex.1039) that Dr. D’Amico relies upon does not provide the underlying data for CLEAR-IT 2, nor does it comment on any differences between the performance of the 2.0 mg and 4.0 mg doses. Dr. D’Amico evidently did not consider the publication of the Brown 2011 study in forming his opinion, but that publication does provide data for both the 2.0 and 4.0 mg dose. In my opinion, the POSA seeking to determine whether increasing the dose of aflibercept was likely to increase its duration of effect would certainly have reviewed and considered data comparing repeated injections of 2 mg and 4 mg doses of aflibercept. I do not know why Dr. D’Amico did not believe this information to be relevant to his analysis. As I explain, the POSA who reviewed the CLEAR-IT 2 results would have concluded that increasing the dose of aflibercept beyond the FDA-approved 2 mg dose was unlikely to produce a clinical benefit to patients.

4. VIEW 1 and VIEW 2

127. Based on CLEAR-IT 2 findings, the study sponsor initiated the Phase III VIEW studies, excluding the 4 mg dose and assigning patients to receive either 0.5 mg or 2 mg. Ex.2089 at 1095. Patients enrolled in the VIEW 1 and VIEW 2 studies received either 0.5 or 2.0 mg of aflibercept at either 4-week or 8-week dosing intervals for the first year of the study. Ex.2090 at 2537. All aflibercept treatment groups achieved statistical noninferiority compared with monthly ranibizumab, meeting the primary endpoints in both studies. Ex.2090 at 2537. In VIEW 1, the proportions of patients maintaining vision were 95.1% (2mg every 4-week), 95.9% (0.5 mg every 4-week), and 95.1% (2mg every 8-week), compared with 94.4% for ranibizumab. Ex.2090 at 2542. In VIEW 2, these proportions were 95.6% (2q4), 96.3% (0.5q4), and 95.6% (2q8), compared with 94.4% for ranibizumab. Ex.2090 at 2543.

128. In the second year, all participants were switched to a capped PRN (as-needed) dosing schedule, receiving at least one injection every 12 weeks at the same dose as in year 1. Ex.2140 at 193. The patients were monitored monthly, and if certain criteria (i.e., worsening visual acuity or increased macular thickness) were met, the patients received more frequent injections than every 12 weeks. Ex.2140 at 193-194. Mean visual acuity gains at week 52 were: 7.9 letters (ranibizumab), 7.6 letters (2mg every 4-week), 6.6 letters (0.5 mg every 4-week), and 7.6 letters (2mg

every 8-week). Ex.2140 at 195-196; Fig. 1. In my opinion, a POSA would conclude with strong confidence that all aflibercept groups had visual acuity outcomes that were non-inferior (not worse) compared with monthly ranibizumab groups in preventing visual acuity loss at 96 weeks. Ex.2140 at 193. The aflibercept 2 mg every 8 weeks regimen in year 1, followed by a capped (12 weeks) PRN regimen in year 2, achieved visual and anatomic results similar to monthly ranibizumab but with approximately five fewer injections over two years. Ex.2140 at 193.

129. Based on these data, the FDA approved 2mg dose aflibercept for neovascular (wet) age-related macular degeneration in 2011. Ex.1053 at 1. The recommended regimen is one intravitreal injection every 4 weeks for the first 3 doses, then one injection every 8 weeks thereafter; some patients may require continued monthly dosing based on clinical response. Ex.1053 at 1. Eylea® 2mg subsequently received FDA approvals for macular edema following retinal vein occlusion, DME, and diabetic retinopathy in patients with diabetic macular edema, among others. Ex.1053 at 1.

130. By May 2018, clinicians—including myself—had been successfully treating patients with approved conditions using the 2 mg dose of aflibercept for about 7.5 years.

5. Additional Aflibercept Safety Data (Clinical and Non-Clinical)

131. Comparison between anti-VEGF agents indicated that different anti-VEGF agents may exhibit different safety profiles associated with structural differences and pharmacokinetic variations. Ex.2085 at 5. For example, ranibizumab is an antibody fragment lacking the Fc domain, making it much smaller than both aflibercept and bevacizumab. Ex.2085 at 5. Because it lacks the Fc domain, ranibizumab also exhibits lower systemic exposure following intravitreal injection. Ex.2085 at 5. In the pharmacokinetic study, aflibercept substantially suppressed circulating plasma-free VEGF with mean levels below the lower limit of quantitation as early as three hours after administration and sometimes, up to more than seven days. In contrast, mean free VEGF levels with ranibizumab were largely unchanged. Ex.2085 at 5. A POSA would have understood these data to suggest that pharmacokinetic variations among non-specific VEGF inhibitors may represent clinically meaningful differences regarding the risk of systemic effects, such as cerebrovascular and cardiovascular events. Ex.2085 at 5.

132. A comparative study similarly found that ranibizumab may offer the “broadest safety profile” among anti-VEGF agents for retinal cells, including aflibercept. Ex.2107 at i15. In this study, researchers directly compared the safety profiles of four anti-VEGF drugs—ranibizumab, bevacizumab, aflibercept, and ziv-aflibercept—using cultured human retinal pigment epithelial cells. Ex.2107 at i12.

The cells were exposed to each drug at 1/2×, 1×, 2×, and 10× clinical concentration for 24 hours. Ex.2107 at i12. Following exposure, the study assessed several indicators of cell toxicity—cell viability, mitochondrial membrane potential (an indicator of early cell death), and media osmolality. Ex.2107 at i12.

133. The study found that among the anti-VEGF drugs tested, ranibizumab best preserves the overall health of retinal pigment cells and, unlike aflibercept, that such effects may be maintained even at higher doses. Ex.2107 at i15. For instance, at 10× clinical concentration, all drugs except ranibizumab reduced cell viability. Ex.2107 at i11. Signs of mitochondrial damage or toxicity were observed at standard doses for bevacizumab and ziv-aflibercept, at 2× and 10× doses for aflibercept, and at 10× for ranibizumab, with no significant changes at lower doses. Ex.2107 at i11. These results would have conveyed to a POSA that multiplying standard doses can cause varying safety effects among different anti-VEGF agents at least in retinal epithelial cells, and that aflibercept, at higher doses, may lead to greater cell toxicity than comparable increases with ranibizumab.

F. Clinical Studies of anti-VEGF Molecules After Aflibercept

134. After Eylea® 2 mg was approved, several new VEGF-molecules were developed and tested in search for a long-acting anti-VEGF molecule that could decrease the treatment burden for patients with nAMD. As of May 2018, none had succeeded.

135. Abicipar, like aflibercept, is a fusion protein, but is a much smaller, non-glycosylated molecule at 34 kDa, whereas aflibercept has a molecular weight of 115 kDa (the non-glycosylated core protein has a weight of about 97 kDa). Ex.2036 at 5837; Ex.1050 at 9. The “small” molecular weight of abicipar “allow[ed] a high molar dose by intravitreal injection, and abicipar has a long intraocular half-life.” Ex.2022 at 1028. Abicipar was administered at the same 50 microliter volume as Eylea®, and owing to its lower molecular weight, the 2 mg dose of abicipar delivered an over threefold higher molar concentration of abicipar as compared to Eylea®’s aflibercept. Ex.2022 at 1028. Investigators hoped that “[t]he optimized combination of high affinity, high molar dose, and long half-life with abicipar may translate into an extended duration of effect after intravitreal injection.” Ex.2022 at 1028.

136. Unfortunately, abicipar never obtained FDA approval and was ultimately abandoned. Abicipar resulted in “significantly higher” inflammation compared to ranibizumab. Ex.2022 at 1032; *see* Ex.2015 at 861:1-15. In 2020, FDA refused to approve abicipar because “the rate of intraocular inflammation observed following administration of Abicipar pegol 2mg/0.05 mL results in an unfavorable benefit-risk ratio in the treatment of neovascular (wet) age-related macular degeneration (AMD).” Ex.2008 at 1. The molecule was then abandoned. *See* Ex.2031 at 1.

137. Beovu (brolucizumab) is another example of failed efforts to obtain longer duration of effect by increasing dose. Brolucizumab is a lower-weight anti-VEGF molecule “with a molecular weight of 26 kDa, allowing for higher molar dosing than previous anti-VEGF therapies.” Ex.2024 at 90. However, in its principal clinical trials, brolucizumab exhibited higher intraocular inflammation than aflibercept: “(4.7% vs. 0.6%).” Ex.2024 at 92. Unlike abicipar, brolucizumab was approved by FDA for administration at a 6 mg dose and 120 mg/ml concentration, Ex.2012 at 1, but its sponsor had to discontinue multiple clinical trials due to inflammation and vision loss, Ex.2032 at 2. In 2020, given patients’ inflammation following brolucizumab injection and, in some cases, “irreversible severe vision loss,” prominent ophthalmologists issued a clear message: “intravitreal injections of brolucizumab should stop.” Ex.2013 at A7. “In the face of the known risk, its use is unwarranted.” Ex.2013 at A8. Accordingly, sales of Beovu have been relatively minimal. Ex.2011 at 1 (quarterly sales of \$39M versus \$1.35B for Eylea).

VIII. Eylea® HD - Aflibercept 8 mg

138. Eylea® HD is not in the prior art and so would not have been available to the POSA as of the May 2018 date relevant here.

139. Eylea® HD is a commercial embodiment of the claimed invention—it is an 8 mg formulation of aflibercept (0.07 mL of 114.3 mg/mL solution) and was

approved in the United States in August 2023. Ex.1054 at 1, 7; Ex.2035 (Eylea® HD FDA Approval Letter) at 1, 6.

140. Eylea® HD delivers a dose four times greater than Eylea® by using a formulation with nearly three times the concentration of aflibercept and an injection volume that is 20 microliters greater. Eylea® HD is approved for the treatment of neovascular AMD, DME, DR, and RVO (the last being a recent indication update). Ex.1054 at 1.

141. Regeneron conducted a proof-of-concept trial (Phase II) evaluating an investigational 8 mg dose of aflibercept and announced its results in a press release on August 24, 2021. Ex.2141 at 1. The FDA's approvals were primarily supported by three global phase III clinical trials: PULSAR for wAMD, PHOTON for DME and DR, and QUASAR for RVO. Ex.1054 at 15-18. In all studies, extended dosing using Eylea® HD achieved clinical non-inferiority end points compared with the standard dose of Eylea® 2 mg, while demonstrating a comparable safety profile between the two drugs. Ex.1054 at 15-18.

142. Eylea® HD offers benefits over other anti-VEGF agents when used on a fixed dosing schedule according to its label. According to its FDA-approved label, the fixed dosing schedule for Eylea® HD is every eight to sixteen weeks (after the loading period), which reduces the average number of required injections when compared with the fixed dosing schedules specified in the labels for ranibizumab or

aflibercept 2 mg. Ex.1054 at 1. The FDA label for ranibizumab recommends 0.5 mg dose as monthly injections for treating wAMD. Ex.1055 at 1. For Eylea® 2 mg, the label recommends an initial loading phase of three monthly injections, followed by injections every eight weeks in the first year followed by a PRN regimen with monthly monitoring and injections at least every 12 weeks in the second year. Ex.1053 at 1. For DME, the FDA label for ranibizumab recommends 0.3 mg dose as monthly injections for two years. Ex.1055 at 1. For Eylea® 2 mg, the label recommends an initial loading phase of five monthly injections followed by injections every eight weeks through two years. Ex. 1053 at 1. The Eylea® HD label allows the extension of the dosing interval to once every 20 weeks after one year of successful response, based on visual and anatomic outcomes. Ex.2131 at 1.

IX. The POSA Would Not Have Been Motivated to Administer an 8 mg Dose of Aflibercept to Treat Angiogenic Eye Disorders With a Reasonable Expectation of Success

143. I have reviewed Alvotech’s Petition and the supporting declarations, which set forth the position that as of May 2018, the POSA would have believed the methods claimed in the ’036 patent to have been obvious in view of various combinations of references. Specifically, I understand Alvotech and Dr. D’Amico to assert that the following claims would have been obvious to the POSA as of May 2018 in view of the following combinations of alleged prior art:

Ground	Claims	Alvotech’s Combination of References
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1	1, 4-38	Vitti, AU Eylea® Label, and Larson
2	1, 4-38	Vitti, AU Eylea® Label, and Larson
4	2, 3	Larson, Vitti, AU Eylea® Label, and 2011 Eylea® Clinical Review
5	2, 3	Furfine, Dix, Fiedler, AU Eylea® Label, Larson and 2011 Eylea® Clinical Review

144. For the reasons explained in more detail below, I disagree with Alvotech’s position as expressed in the Petition and in Dr. D’Amico’s declaration.

145. As reflected above, every one of the challenged claims requires a dose of at least 8 mg aflibercept. As I explain in detail below, the POSA would not have been motivated to administer doses of 8 mg aflibercept to treat angiogenic eye disorders because nothing in the prior art suggested that doing so would confer benefits over the existing 2 mg dose—to the contrary, the prior art suggested an 8 mg dose would *not* have provided such benefits.

146. In addition, the prior art would have taught the POSA that there were reasons to be concerned about the safety of an 8 mg dose—thereby teaching away from pursuing such a dosing strategy, particularly in the absence of any expectation of clinical benefit.

1. The AU Label Would Not Have Motivated the POSA to Administer an 8 mg dose of Aflibercept, Alone or in Combination with Vitti

147. In Ground 1, Dr. D’Amico opines that a combination of the AU Label and Vitti would have motivated the POSA to administer an 8 mg dose of aflibercept with a reasonable expectation of success. In Ground 2, Dr. D’Amico relies only on the AU Label for the POSA’s motivation to administer an 8 mg dose. I disagree that the POSA would have had reason to administer an 8 mg dose on the basis of the AU Label or Vitti, alone or in combination.

148. Dr. D’Amico stated in his declaration that “[a] POSA would have further believed an 8 mg dose of aflibercept would be capable of treating patients with AMD, DME, and DR given the clinical trial discloses [*sic*] in the AU Eylea® Label.” Ex.1003 ¶ 170. Dr. D’Amico’s deposition further confirms the centrality of the AU Label to his 8 mg theory: he testified that his opinion that a POSA would have wanted to use 8 mg aflibercept had its “primary impetus” in the Australian label. Ex.2053 (D’Amico Dep. Tr.) at 324:14-23. He later reiterated that the “initial impetus” for his selection of the 8 mg dose was the Australian label. Ex.2053 at 327:7-17.

149. In my opinion, the AU Label would not have motivated the POSA to administer intravitreal injections of 8 mg of aflibercept; to the contrary, it would have discouraged the POSA from doing so.

150. The AU Label provides product information for the 2 mg, 40 mg/ml Eylea® formulation as approved by the Australian Therapeutic Goods Agency (i.e., the Australian equivalent of the FDA). Ex.1009 at 2, 35. With respect to the dosage and administration of aflibercept, it recommends the following:

DOSAGE AND ADMINISTRATION

EYLEA is for intravitreal injection only.

It must only be administered by a qualified ophthalmologist experienced in administering intravitreal injections.

Dosage regimen

The recommended dose for EYLEA is 2 mg aflibercept, equivalent to an injection volume of 50 µL. The interval between doses injected into the same eye should not be shorter than one month.

Ex.1009 at 29. In my opinion, 2 mg is the only dose that the AU Label would have *motivated* the POSA to administer. The purpose of a drug label is to instruct physicians as to how to use the drug safely and effectively. The AU Label instructs clinicians to administer 2 mg of Eylea® in a volume of 50 microliters—in my opinion, that is precisely what the POSA reading the AU Label as of May 2018 would have done.

151. In his declaration, Dr. D’Amico offers the opinion that the POSA reading the AU label would have been motivated to administer an 8 mg dose of aflibercept, because that dose is referred to in the “OVERDOSAGE” section of the AU Label, as follows:

OVERDOSAGE

In clinical trials doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated. Overdosing was associated with increased injection volume and subsequently with increased intraocular pressure. Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated. It is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

Ex.1009 at 35. When asked whether he “rel[ies] on the overdosage section of this Australian label to support [his] opinion that the skilled person would have been motivated to use a dose of aflibercept that is 8 milligrams,” he answered “[c]orrect.”

Ex.2053 at 399:10-16. When asked about the meaning of “isolated cases” and “generally well tolerated,” he admitted it could be any number more than two,

Ex.2053 at 402:24-403:5, and he stated “generally well tolerated” means “there was no additional toxicity associated with that dose” and the patients “did not lose the eye,” “did not have rip-roaring retinitis” and “did not have vision decrease.”

Ex.2053 at 405:4-14 (cleaned up). I agree that his characterization fits the POSA’s understanding of the term “generally well-tolerated,” but his interpretation only goes to show that “generally well-tolerated” does not amount to an endorsement of the drug’s safety. Thus, I disagree with Dr. D’Amico’s assertion that such general tolerance—“no additional toxicity,” “did not lose the eye”—would motivate a POSA to pursue the 8 mg dose with any confidence that it offers improved efficacy, durability, or safety compared to the 2 mg dose.

**a. The AU Label Would Not Have Given the POSA
Any Reason to Expect Benefits from an 8 mg
Dose**

152. Dr. D’Amico asserts that the POSA would have been motivated to pursue an 8 mg dose of aflibercept because the AU Label suggested such a dose would have been safe. I disagree, for all the reasons set forth below. Regardless, Dr. D’Amico’s focus on the AU Label for its supposed teaching that an 8 mg dose is not deleterious overlooks an important issue—nothing in the AU Label suggests the 8 mg dose has a benefit. The POSA would not have had reason to administer *any* dose of aflibercept other than 2 mg in 50 microliters *unless* the POSA had reason to believe such a dose would have a clinical advantage (i.e., better efficacy or longer duration) over the FDA-approved 2 mg dose. Both available clinical data (i.e., CLEAR-IT 2), *see supra* §VII.E., and the AU Label suggest the opposite. As I explained above, the AU Label recommends a dose of 2 mg aflibercept. The fact that it does so despite reference to clinical trials evaluating 4 mg doses of aflibercept would have communicated to the POSA that even though higher doses of at least 4 mg had been explored, the 2 mg dose had been determined to be the clinically appropriate one. Because the AU Label teaches the POSA that a higher dose of aflibercept (i.e., 4 mg) had been tested in trials but abandoned—and indeed that was the case, as I describe below with respect to the CLEAR-IT studies—the POSA

would have inferred that increasing the aflibercept dose above 2 mg had not demonstrated clinical superiority in visual acuity or duration.

b. The AU Label Would Not Have Caused the POSA to Expect Safety from an 8 mg Dose

153. Dr. D’Amico testified at deposition that “[w]e knew that 8 milligrams was safe.” Ex.2053 (D’Amico deposition), 220:20. I disagree with Dr. D’Amico’s statement, especially since it appears to be primarily based on reports of “isolated cases” of 8 mg overdose. The term “Overdosage” alone conveys to a POSA that a medication error has occurred. In fact, the FDA requires drug overdoses to be reported in the FDA Adverse Event Reporting System, as the FDA explicitly defines “overdose whether accidental or intentional” as “an adverse event.” Ex.2111 at 1-2. Dr. D’Amico has also testified in other contexts that information far more detailed than the single statement in the AU Label would *not* be sufficient to provide an inference of safety. For example, when presented with a report stating that six patients accidentally received a three-fold intracameral cefuroxime overdose, were followed closely for six months, and had “no significant change in ocular findings,” Dr. D’Amico still denied that the report would provide a reason to administer that higher dose in the future. Ex.2053 (D’Amico Dep. Tr.) at 131:16-132:23, 133:23-134:22. He explained that “[t]hese people happened to get lucky” and later characterized the report as “an isolated report out of Turkey with incomplete details regarding a drug dosage” that would not cause him to “suddenly change [his]

medical practice” or administer a higher dose in the future. Ex.2053 (D’Amico Dep. Tr.) at 134:19-135:24, 141:23-142:12.

154. Dr. D’Amico’s opinion overlooks the language immediately following reference to “isolated cases” of 8 mg overdose—far from encouraging the POSA to use an 8 mg overdose, the AU label teaches away from doing so, because it advises “contact[ing] the Poisons Information Centre (131 126) for recommendations on the management and treatment of overdose.” Ex.1009 at 35. Dr. D’Amico does not acknowledge this statement anywhere in his declaration. In my opinion, the POSA would not have been motivated to undertake activities that a healthcare agency characterizes as a potential poisoning event.

155. Even setting aside the AU Label’s warning *not* to overdose patients, the single statement in the AU Label that “isolated cases” of overdose were “well-tolerated” cannot support a statement that “we knew 8 mg was safe” as of May 2018. To the contrary, clinicians in May 2018 did not “know” anything about an 8 mg dose of aflibercept, other than that “in isolated cases” (a statement the POSA would have understood to mean “in at least two cases”) the dose was well-tolerated—i.e., did not cause negative outcomes that were clearly observable on the basis of whatever undisclosed monitoring these at least two patients received, for whatever undisclosed duration that monitoring occurred.

156. As a practical matter, all the POSA could have inferred from this statement as of May 2018 was that in at least two instances, patients did not go blind or suffer an obvious deterioration of vision health after receiving an accidental 8 mg dose of aflibercept. Far from understanding the AU Label to teach or suggest that 8 mg of aflibercept *should* or *could* be safely administered to patients, the POSA instead would have understood that in the isolated cases described in the AU Label, the overdosed individuals (and their clinicians) happened to get lucky and no obvious harm was done, and that the safety of such doses, however, remains to be evaluated in clinical trials.

157. Indeed, “[t]hese people happened to get lucky” is precisely how Dr. D’Amico described the result of a *different* ocular drug overdose in the context of antibiotic injections into the intracameral space in the eye. Ex.2053 (D’Amico Dep. Tr.) at 133:23-135:24 (discussing Ex.2044). In that case, Dr. D’Amico denied that a single, well-tolerated, accidental triple-dose of the antibiotic cefuroxime would have motivated the POSA to pursue a triple dose of cefuroxime in the future, even in patients who he agreed cefuroxime injections were appropriate or required, because he viewed it as an isolated report with incomplete details that would require

confirmation before changing practice.³ Ex.2053 (D’Amico Dep. Tr.) at 132:25-133:22, 137:5-138:6, 141:22-142:12.

158. In my opinion, this testimony is inconsistent with Dr. D’Amico’s reliance on the AU Label. Dr. D’Amico faulted the cefuroxime report because it involved “a single clinic in ... Turkey with authors unknown to me with incomplete information of who prepared this formulation and how sure were they of the 3 milligram dosage.” Ex.2053 (D’Amico Dep. Tr.) at 141:10-18. Dr. D’Amico said he “would give ... the data in this [cefuroxime] report very different credence to what I might give a -- a more rigorously conducted trial with, you know, multiple observations.” Ex.2053 (D’Amico Dep. Tr.) at 141:2-9. He went on to note that “the quality of the data is ... assigned a value by how many publications reproduce this result, what is the quality of the people who’ve gone into it, how thorough is their documentation, what are their subsequent follow-up presentations regarding this, et cetera.” Ex.2053 (D’Amico Dep. Tr.) at 143:5-14. All of the shortcomings Dr. D’Amico found in the cefuroxime report are equally true of the statement in the AU Label—if anything, the cefuroxime report contains far more detailed

³ As relevant here, cefuroxime is a prophylactic antibiotic administered after cataract surgery. I understood Dr. D’Amico to testify that he disagrees that many or even most patients require such prophylaxis after cataract surgery but agreed that certain patients do require antibiotic administration. I understood him to say that he would not have reason to increase the dose of cefuroxime based on the overdose report *even* in patients who indisputably require cefuroxime.

information regarding the manner in which the overdosed patient was monitored than the AU Label does. In fact, Dr. D’Amico admitted that he did not know who administered the 8 mg overdose, where it occurred, whether it occurred in Turkey, or what procedures were used, and that the AU Label provided no underlying data showing what effect the overdose had—only the bare assertion that it was “generally well tolerated.” Ex.2053 (D’Amico Dep. Tr.) at 405:25-407:21.

159. The AU Label provides no details about how the overdoses occurred, making it impossible for a POSA to assess or characterize the associated risks. For example, the AU Label does not specify whether the referenced 8 mg aflibercept overdoses occurred in a single, isolated clinic, whether that clinic had ophthalmologists with extensive experience with intravitreal injections, how sure the physicians were that an overdose occurred, who prepared the injections that led to the use of a syringe containing four times the dose and potentially four times the volume. Nor am I aware of *any* publications that reproduce the overdose results from the AU Label, any presentations regarding those overdoses, any information on the “quality of the people” who administered or reported the overdoses, the thoroughness of their documentation, or for how long or in what way the overdosed patients were followed. Ex.2053 (D’Amico Dep. Tr.) at 404:25-408:9. Certainly, the AU Label contains none of this information, nor is it a “rigorously conducted

trial” of the kind Dr. D’Amico referenced when contrasting the report of a cefuroxime overdose.

160. Regardless, the POSA would not have read the AU Label and been motivated to pursue a treatment strategy based on a single statement that “isolated cases” of an 8 mg overdose was “generally well tolerated.” In the Petition, Alvotech asserts that Regeneron has relied on this “overdose” data as justification for the 8 mg dose for Eylea HD. Pet. at 19 (“Tellingly, Regeneron itself has relied on this ‘overdose’ data to justify its EYLEA HD, 8 mg aflibercept indication.”). As the study sponsor, Regeneron likely had access to information about how the overdoses occurred and the specific details of how an 8 mg overdose was “generally well tolerated”—information, as previously discussed, not available to the public or to a POSA. *See also* Ex.2053 at 410:15-411:5 (Dr. D’Amico assuming Regeneron would have information about “how many cases of overdoses there were, what happened to those patients, for how long they were monitored, et cetera”). With knowledge of the circumstances of the overdoses, including the number of patients who received 8 mg injections, injection volume, how the overdoses happened, and detailed follow-up data, Regeneron could have made an informed decision about the 8 mg dose. However, a POSA, lacking that information, could not have reached the same conclusion.

161. Moreover, as the POSA would have been aware, and as Dr. D’Amico acknowledged, patient responses to drug therapy—including anti-VEGF agents used to treat conditions such as AMD—are variable, and clinicians cannot predict in advance how a given patient will respond or how frequently they will need to be treated. Ex.2053 at 146:3-147:5, 150:19-151:8. I cannot predict, ex ante, in any given patient receiving an anti-VEGF agent, how often that patient will need to receive injections (or whether they will respond to the drug at all), whether the patient will tolerate repeated exposure to the anti-VEGF agent I have chosen, whether the patient will experience a damaging spike in intraocular pressure during an injection, or the incidence of any other unwanted side effect. As the POSA would have understood, certain subgroups of patients, on average, were known to be more susceptible to certain adverse reactions—e.g., following the same intravitreal injections and the corresponding increase in intraocular pressure, patients with greater perfusion pressure of the retinal artery are more prone to transient vision loss, and patients with low tension glaucoma face greater risk of optic nerve damage. Those patients are important recipients of anti-VEGF agents such that the POSA would not have been motivated to pursue a drug that could not safely be administered to them, but the POSA would have had no way of knowing whether those vulnerable populations were represented in the “isolated cases” of 8 mg aflibercept overdoses.

162. Even if the AU Label had provided the POSA with more information about what adverse events were monitored and for how long before concluding that the isolated cases of 8 mg overdose had been “generally well-tolerated,” the POSA would have understood that this small number of patients is simply insufficient to create any expectation of safety in a broader population. For example, if just 10 patients were given 8 mg and no serious adverse events were noted, the rule of three indicates that there is 95% confidence that the true rate of a serious adverse event is no greater than $3/n$, where n is the number of cases evaluated. Ex.2105 at 1744. In this scenario, $3/10$ equals 30%, meaning there is a 95% confidence that the true rate of serious adverse events is no greater than approximately 1 in 3 injections—hardly a risk any POSA would be willing to accept. Thus, “isolated 8 mg overdoses” reflects such a small sample size as to provide virtually no meaningful safety assurance for routine clinical use of the 8 mg dose. Dr. D’Amico’s deposition testimony reinforces this point. When asked whether an isolated accidental overdose of another intraocular medication would provide a reason to administer the higher overdose amount in the future, he answered, “No” and “Not at all,” emphasizing that an isolated report with incomplete details would not cause him to change medical practice. *See* Ex.2053 (D’Amico Dep. Tr.) at 132:16-133:17, 141:22-142:12.

163. A POSA would further recognize the importance of enrolling a sufficient number of patients to account for safety variability. For example,

enrolling 300 patients would, under the rule of three, provide at least 95% probability of detecting any serious adverse events with a frequency of 1% or higher ($3/n = 3/300 = 1\%$). Nevertheless, the POSA would understand that post-marketing surveillance is still necessary to identify serious adverse events that may not have been detected during phase 3 clinical trials.

164. Dr. D’Amico does note the AU Label’s statement “[o]verdosing was associated with increased injection volume and subsequently with increased intraocular pressure.” Ex.1003 ¶ 62 (quoting Ex.1009 at 35). Dr. D’Amico states, without any actual support, that “a POSA would understand the only concern it identifies is increased interocular pressure from the ‘increased injection volume’ associated with quadrupling the 2 mg dose (at 50 microliters) to 8 mg (which would be a volume of 200 microliters),” and not that “the 8 mg dose itself caused any concerns with efficacy or safety.” Ex.1003 ¶¶ 198, 295. However, the AU Label does not explain how overdosage occurred. Although it is plausible that injection volume increased in these accidental overdoses, the AU Label does not specify how far apart the injections were or whether the aflibercept concentration remained consistent across all injections. Therefore, a POSA could not have assumed that quadrupling the dose necessarily resulted in a quadrupled volume and that any observed spikes in intraocular pressure were solely attributable to increased volume.

2. Vitti Would Not Have Motivated the POSA to Pursue an 8 mg Aflibercept Dose

165. Alvotech asserts that the POSA would have selected 8 mg aflibercept because Vitti discloses “0.05 mg to about 10 mg of a VEGF antagonist (e.g., aflibercept)” Pet. 29; Ex.1007, ¶139. In my opinion, the only dose of aflibercept Vitti explicitly discloses is 2 mg. *E.g.*, Ex.1007 ¶¶ 264-267, 270. The disclosed range of “0.05 mg to about 10 mg of a VEGF antagonist” contains nearly 1000 discrete aflibercept doses in 0.01 mg increments, or nearly 200 in 0.05 mg increments. I am informed by counsel that there is no presumption of obviousness when the prior art range is so broad as to encompass a very large number of possible distinct compositions.

166. Though Dr. D’Amico does not reference that disclosure when discussing the 8 mg disclosure, he nonetheless states that Vitti teaches formulations with a dose of “at least about 8 mg” or “about 8 mg” primarily because of Vitti’s concentration disclosures. Ex.1003 ¶¶ 196-97, 251. The full paragraph in Vitti, upon which Dr. D’Amico relies in part, states:

In certain embodiments, the pharmaceutical formulations are liquid formulations that may contain 5-0.75 mg/mL to 100+15 mg/mL of a VEGF antagonist. For example, the formulations of the present invention may comprise about 5 mg/mL; about 10 mg/mL; about 15 mg/mL; about 20 mg/mL; about 25 mg/mL; about 30 mg/mL; about 35

mg/mL; about 40 mg/mL; about 50 mg/mL; about 60 mg/mL; about 70 mg/mL; about 80 mg/mL; about 90 mg/mL; or about 100 mg/mL of a VEGF antagonist such as aflibercept.

Ex.1007 ¶ 94.

167. Vitti defines the term “VEGF antagonist” in paragraph 85 as follows:

As used herein, a “VEGF antagonist” is any agent that binds to or interacts with VEGF, inhibits the binding of VEGF to its receptors (VEGFR1 and VEGFR2), and/or inhibits the biological signaling and activity of VEGF. VEGF antagonists include molecules which interfere with the interaction between VEGF and a natural VEGF receptor, e.g., molecules which bind to VEGF or a VEGF receptor and prevent or otherwise hinder the interaction between VEGF and a VEGF receptor. Specific exemplary VEGF antagonists include anti-VEGF antibodies (e.g., ranibizumab LUCENTIS(R), anti-VEGF receptor antibodies (e.g., anti-VEGFR1 antibodies, anti-VEGFR2 antibodies, etc.), small molecule inhibitors of VEGF (e.g., Sunitinib), and VEGF receptor based chimeric molecules or VEGF-inhibiting fusion proteins (also referred to herein as “VEGF-Traps”).

Ex.1007 ¶ 85.

168. The POSA would understand the definition to convey that “VEGF antagonist” refers to a genus of many different molecules—i.e., not just aflibercept.

This definition is consistent with the plain and ordinary meaning of the term “VEGF antagonist” to the POSA as of May 2018. Thus, when Vitti refers in paragraph 94 to “liquid formulations that may contain 5 ± 0.75 mg/mL to 100 ± 15 mg/mL of a VEGF antagonist”, I interpret that sentence to disclose liquid formulations of VEGF antagonists as Vitti broadly defines them, not just aflibercept.

169. Likewise, the paragraph 94 of Vitti states:

For example, the formulations of the present invention may comprise about 5 mg/mL; about 10 mg/mL; about 15 mg/mL; about 20 mg/mL; about 25 mg/mL; about 30 mg/mL; about 35 mg/mL; about 40 mg/mL; about 50 mg/mL; about 60 mg/mL; about 70 mg/mL; about 80 mg/mL; about 90 mg/mL; or about 100 mg/mL of a VEGF antagonist such as aflibercept.

The POSA would have understood that disclosure—and in particular the final language “or about 100 mg/mL of a VEGF antagonist *such as aflibercept*” (emphasis added) to refer to formulations of VEGF antagonists, *including but not limited to aflibercept*, of about 100 mg/mL. Vitti also defines the term “about”:

As used herein, the term “about,” when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression “about 100” includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

Ex.1007, ¶ 48. Thus, I understand Vitti's disclosure of "about 100 mg/mL of a VEGF antagonist such as aflibercept" to refer to VEGF antagonist formulations ranging from 99 mg/mL to 101 mg/mL, since "about" was defined as plus or minus one percent. In my opinion, the POSA would not have interpreted any of these disclosures of *concentrations*—including the concentrations of 80, 90, and 100 mg/mL—to teach or suggest an 8 mg dose, let alone an 8 mg dose in an injection volume of 70 µL.

170. Concentration is equal to dose divided by volume. For example, if the POSA knows a formulation's concentration, the POSA can multiply that value by the volume of administration to calculate the dose. Claims 31-34 require an injection volume of 70 µL and a dose of about 8 mg, both of which Dr. D'Amico asserts would have been obvious. Ex.1003 ¶¶ 251, 254. However, Dr. D'Amico's declaration does not provide any additional analysis with respect to the 8 mg limitation in claim 31—instead, it merely incorporates by reference his opinions with respect to claims 1 and 27—and the analysis for those claims assumes an injection volume of 100 µL. Ex. 1003 ¶¶195-198 (claim 1), 245 (claim 27), 251 (claim 31). Specifically, Dr. D'Amico argues that Vitti's disclosures of 80 mg/ml, 90 mg/ml, and 100 mg/ml also discloses doses at and above 8 mg because, at 100 µL, an 80 mg/ml formulation has an 8 mg dose ($80 \text{ mg/ml} * 0.1 \text{ ml}$), 90 mg/ml has a 9 mg dose ($90 \text{ mg/ml} * 0.1 \text{ ml}$), and 100 mg/ml has a 10 mg dose ($100 \text{ mg/ml} * 0.1 \text{ ml}$). Ex.1003 ¶¶ 196-197.

171. On the other hand, if you do those same calculations with the assumption the POSA would use a 70 μ L volume, you get doses of 5.6 mg (80 mg/ml * 0.07 ml), 6.3 mg (90 mg/ml * 0.07 ml), and 7 mg (100 mg/ml * 0.07 ml). Thus, Vitti's disclosures of 80 mg/ml, 90 mg/ml, 100 mg/ml do *not* disclose an 8 mg dose at an injection volume of 70 μ L, as required by claims 31-34.

172. Moreover, rather than teaching the use of a high dose of aflibercept, Vitti teaches extending dosing intervals by combining a VEGF antagonist with a separate Ang-2 inhibitor (mAb1):

According to another aspect of the present invention, methods are provided for ***reducing the dependence and treatment burden of frequent intravitreal injections in a Subject with a vascular eye disease or disorder***. The methods comprise sequentially administering an initial dose followed by one or more secondary doses of a therapeutically effective amount of ***a pharmaceutical composition comprising an Ang-2 inhibitor in combination with a VEGF antagonist to the subject in need thereof; wherein the administration of the pharmaceutical composition is reduced to once every 9 weeks as compared to a subject who has been administered the VEGF antagonist alone***.

Ex.1007 ¶ 15 (emphasis added). This approach is reiterated throughout Vitti, including in the abstract, which states: "The methods of the present invention comprise administering to a subject in need thereof a therapeutic composition comprising an angiopoietin-2 (Ang-2) inhibitor such as an anti-Ang-2 antibody in combination with a vascular endothelial growth factor (VEGF) antagonist (e.g., aflibercept)." Ex.1007 at 1. Thus, Vitti teaches the POSA that, if the POSA wants to use a VEGF antagonist, the path to extended dosing is through combination

VEGF/Ang-2 inhibition—not through increasing the dose or concentration of aflibercept.

173. Additionally, nothing in Vitti would have pointed the POSA to an 8 mg dose from within the broad disclosed range—every example that included stability or clinical data used 2 mg. Ex.1007 ¶¶ 197-217 (Example 7), ¶¶ 227-29 (Example 9), ¶¶ 230-308 (Example 10). If the POSA looked to Vitti to select a dose of aflibercept to use to treat angiogenic eye disorders, they would have picked the dose supported by this stability data, i.e. 2 mg.

174. In my opinion, for the reasons discussed above, if a POSA looked at Vitti to select a dose of aflibercept to use to treat angiogenic eye disorders, a POSA would not have selected 8 mg aflibercept.

3. The Prior Art as a Whole Would Not Have Motivated the POSA to Pursue an 8 mg Dose of Aflibercept with a Reasonable Expectation of Success

175. In my opinion, the prior art as a whole would not have motivated the POSA to pursue an 8 mg dose of aflibercept with a reasonable expectation of success. After reviewing the references cited by Dr. D’Amico, I do not find any evidence supporting the clinical benefit or safety of the 8 mg dose, as of May 2018. Based on my experience and review of the relevant literature, I would not, as of May 2018, have expected the 8 mg dose to offer additional benefit or to be safely administered to patients.

176. Dr. D’Amico cites two Phase I trials—Nguyen 2009 (Ex.1034) and Nguyen 2012 (Ex.1035)—where 0.5 mg and 4 mg doses were tested to broadly support that “the safety and tolerability of 0.5 mg and 4 mg doses of aflibercept were identical (Ex.1035);” and “higher doses were safe, effective, and well tolerated per Nguyen 2009 (Ex.1034).” Ex.1003 ¶¶ 167 (Ex.1035), 272 (Ex.1034). However, both studies were Phase I trials with limited sample sizes: Nguyen 2009 included 21 participants, with only 3 participants assigned to each dose group, while Nguyen 2012 included 28 participants, with 14 assigned to the dose group. Ex.1034 at 2141; Ex.1035 at 1035. Each patient received a single intravitreal injection and was evaluated only at short follow-up intervals—6 and 12 weeks in Nguyen 2009, Ex.1034 at 2141, and week 8 in Nguyen 2012, Ex.1035 at 1035. In Nguyen 2009, efficacy and safety data for the 2 mg and 4 mg doses were only reported as combined results, and a POSA could not have made any comparisons between 2 mg and 4 mg doses. Ex.1035 at 582-583. In Nguyen 2012, the study compared only the lowest and highest doses—0.15 mg and 4 mg—so it did not include a comparison between 2 mg and 4 mg groups and was therefore an insufficient study for dose-response assessment. Ex.1035 at 582-83. In other words, Nguyen 2012 could not have informed a POSA whether a dose between 0.15 mg and 4 mg, including the standard dose of 2 mg, would be more or less efficacious, or safer.

177. Additionally, Dr. D’Amico acknowledged that CLEAR-IT 1 involved a single injection and far fewer patients than CLEAR-IT 2. Ex.2053 at 270:22-271:7. A POSA would have recognized that the observation of “identical” safety and tolerability profiles for the 0.5 mg and 4 mg doses in a single, small Phase I study does not imply that higher doses, such as 8 mg, would be more successful than the FDA-approved 2 mg dose. On the contrary, a POSA would have known that further studies are necessary to evaluate the safety and efficacy of aflibercept across a broad range of doses, including 0.5 mg and 4 mg.

178. Dr. D’Amico also cites “Lehman Presentation,” which discusses the outcome of Phase I CLEAR-IT 1 trial. Ex.1003 ¶ 167. The Lehman Presentation consists of a single slide and does not report the full data from the study. Ex.1030 at 18. This slide lacks even the minimum information necessary to evaluate validity of its conclusion. Ex.1030 at 18. Slide 18 merely states, “3-6 subjects given single intravitreal injection to determine maximum tolerated dose,” and “[a]ll planned dose level completed: maximum tolerated dose not reached.” Ex.1030 at 18. It omits all relevant data, such as baseline visual acuity, retinal thickness, and subject outcomes, preventing a POSA from drawing any conclusion as to whether the maximum tolerated dose was reached.

179. Even if a POSA accepted the assertion that the “maximum tolerated dose [for aflibercept] was not reached” following administration of 2 mg and 4 mg

doses of aflibercept, a POSA would still have not believed that such conclusion implies higher doses, such as 8 mg, would be more successful than the tested 4 mg. Ex.1030 at 18. The maximum tolerated dose (MTD) refers to the highest dose of a drug or treatment that can be administered to patients without causing unacceptable or dose-limiting toxicities. Ex.2091 at 709. Because the traditional MTD approach focuses on dose-limiting toxicities—often defined as the occurrence of severe adverse events (typically Grade 3 or higher) in two or more patients within a dose cohort—it may not fully account for therapeutic efficacy or for later-occurring or lower-grade events that affect how patients could reasonably tolerate treatment over time. Ex.2092 at 1318-1319; Ex.2113 at 2040-2041. This limitation is particularly relevant for targeted therapies such as aflibercept, where dose-limiting toxicities may not appear even at doses above those needed for biological activity, and where alternative dose-selection approaches may be needed to identify an appropriate dose. Ex. 2092 at 1318-1319, 1321-1322. A POSA would have been well aware that such agents frequently achieve maximum efficacy at doses well below the maximum tolerated dose, meaning that dose escalation to the toxicity ceiling may expose patients to unnecessary harm without conferring additional therapeutic benefit. Ex.2092 at 1318-1320.

180. Despite the lengthy discussion of the Phase I clinical trial, Dr. D’Amico notably omits any discussion of the Phase II CLEAR-IT 2 trial, which involved a

substantially larger patient population (159 patients compared to just 21), and a more rigorous evaluation of efficacy and safety. Ex.2089 at 1089-1090. During his deposition, Dr. D'Amico agreed that CLEAR-IT 2 was "certainly germane" to the issue of whether higher-dose aflibercept would have a longer duration of action, that CLEAR-IT 2 had "159 patients" compared to CLEAR-IT 1's "21 patients," and that CLEAR-IT 2 involved multiple injections whereas CLEAR-IT 1 involved only a single injection. Ex.2053 (D'Amico Dep. Tr.) at 270:10-271:7.

181. In the CLEAR-IT 2 study, patients were randomized to receive 0.5 mg or 2 mg administered every four weeks (monthly dosing on day 1 and at weeks 4, 8, and 12), or 0.5 mg, 2 mg, or 4 mg administered every 12 weeks (quarterly dosing on day 1 and at week 12). Ex.2089 at 1090. The study demonstrated that at week 12, increasing the dose of aflibercept from 0.5 mg to 2 mg did not confer a clinically meaningful advantage. Ex.2089 at 1089-1090, 1093. At week 12, the mean BCVA improvements for the every 4-week groups were numerically worse in the 2 mg group than in the 0.5 mg group, though the difference was not clinically meaningful: 8.8 letters (SD $\pm$ 9.2) in the 0.5 mg group and 8.3 letters (SD $\pm$ 10.1) in the 2 mg group. Ex.2089 at 1093, Fig. 3. A POSA would have understood from these results that aflibercept lacks a dose-response relationship favoring a higher-dose 2 mg regimen at week 12 or 16. During the PRN phase (week 12 through week 52), patients continued to receive the same dose as their initially assigned dose, but on

an as-needed basis. Ex.2118 at 1099. The results showed that the 2 mg group (initially administered every four weeks) showed better visual acuity outcomes than all other groups, including the 0.5 mg groups (initially administered every four weeks) or the 4 mg group (initially administered every twelve weeks). Ex.2118 at 1102, Fig. 5B.

182. There was no evidence that extra anti-VEGF drugs were “lying in wait,” rather than being degraded or metabolized. Clinical trial data available at that time showed that 4 mg aflibercept is not as clinically effective and showed no indication that it may be more “durable” than 2 mg aflibercept. Dr. D’Amico likewise admitted in his deposition that he did not specifically describe in his declaration the duration of effect of the 4 mg dose compared with the 2 mg or 0.5 mg doses. Ex.2053 at 274:11-18.

183. As Dr. D’Amico described in his declaration, the treatment burden of these injections was widely recognized, prompting various efforts by clinicians and drug companies to address it. Ex.1003 ¶¶ 74-76 (quoting Ex.1047). Some attempted to minimize the number of injections by using PRN (as-needed) dosing, EX1026 at 2182, while others, as discussed below, explored administering higher doses of anti-VEGF agents to extend dosing intervals. However, none of those studies at the time demonstrated that increasing the dose could lengthen dosing intervals, decrease the number of doctor visits or improve clinical efficacy.

184. A study investigating another VEGF agent, bevacizumab (Avastin®), found that increasing the dose does not enhance efficacy and may worsen adverse effects. In this randomized study, 86 patients received either 1.25 mg or 2.5 mg of bevacizumab for choroidal neovascularization (CNV) associated with AMD. Ex.2106 at 102. The results showed no statistically significant difference in improvements in visual acuity or reduction in foveal thickness. Ex.2106 at 102. The mean improvement in BCVA was 0.06 ± 0.3 logMAR in the 1.25 mg group and 0.07 ± 0.34 logMAR in the 2.5 mg group ($P=0.9$). Ex.2106 at 102. The mean decrease in foveal thickness was 49 ± 36 μ m in the 1.25 mg group and 65 ± 31 μ m in the 2.5 mg group ($P=0.6$). Ex.2106 at 102. Similar proportions of patients in each group gained at least 3 lines of BCVA (25.5% vs. 23.1%, $P=0.7$) or lost more than 3 lines (12.8% vs. 10.3%, $P=0.7$). Ex.2106 at 104.

185. In contrast to the 1.25 mg group, which reported no adverse events, the higher dose, 2.5 mg group experienced several complications. Ex.2106 at 104-05. Notably, three cases (7.7%) of clinically significant vitritis, the inflammation of the vitreous body, occurred within 48 hours in the 2.5 mg group, all accompanied by decreased visual acuity and trace anterior chamber reaction. Ex.2106 at 104. Additionally, two patients (5.1%) in the 2.5 mg group developed acute posterior vitreous detachment associated with pinpoint peripheral retinal hemorrhages. Ex.2106 at 104-105. Another patient with predominantly classic CNV developed

sudden visual loss six days after the bevacizumab injection due to massive subretinal hemorrhage. Ex.2106 at 105. Thus, the study concluded that “2.5 mg [bevacizumab] to be equally effective as 1.25 mg but the higher dose seems to be associated with more adverse effects.” Ex.2106 at 106.

186. Dr. D’Amico cites Stewart (Ex.1039) as “suggest[ing] that increasing the dose of a drug prolongs its duration of action.” Ex.1003 ¶ 172 (quoting Ex.1039 at 1182). Stewart makes it clear that the quoted statement is a speculation, rather than reflecting any conclusion, or consensus by a POSA. Ex. 1039 at 1182 (“Both trials suggest, *but do not prove*, that increasing the dose of a drug prolongs its duration of action (durability).”) Stewart notes that “[b]ecause aflibercept has been used for only a short period of time since approval, surgeons cannot accurately determine its durability, nor can they determine if the treatment interval can be extended beyond 8 weeks.” Ex.1039 at 1181. Further, full results for the “trials” Stewart references (VIEW 1/VIEW 2 and HARBOR) had not been published when Stewart was written. Ex.1039 at 1181 n.113, 1182. At most, Stewart’s hypothesis turns on a small difference, without appropriate statistical analyses, from preliminary data in the number of injections patients received on different doses of ranibizumab, and is belied by conclusions drawn from subsequently published publications reporting the primary outcomes in 2013, as well as additional outcomes published in 2014.

187. The HARBOR trial was a phase III study evaluating the efficacy and safety of ranibizumab at 0.5 mg and 2.0 mg doses, administered either monthly or as needed (PRN). Ex.1026 at 2182. The study was designed to assess whether a higher dose or PRN dosing provided additional benefits compared to the established 0.5 mg monthly regimen. Ex.1026 at 2182. During the initial loading phase, all patients received three consecutive monthly doses of intravitreal ranibizumab (0.5 mg or 2.0 mg). Ex.1026 at 2183. Afterwards, patients in the monthly groups continued to receive monthly injections, while those in the PRN groups were evaluated and re-treated based on clinical assessment at each monthly visit. Ex.1026 at 2183.

188. The HARBOR study did not show that anti-VEGF's duration can be extended by increasing its dosage. A key finding of the HARBOR trial was that increasing the ranibizumab dose to 2.0 mg—a four-fold increase—did not provide additional visual acuity benefits or superior clinical outcomes compared to the approved 0.5 mg dose. Ex.1026 at 2190. At month 24, mean BCVA gains were +9.1 letters (0.5 mg monthly) versus +8.0 letters (2.0 mg monthly), and +7.9 letters (0.5 mg PRN) versus +7.6 letters (2.0 mg PRN). Ex.1026 at 2181. While patients in the higher-dose PRN group may have required fewer injections, the difference was also minimal. Ex.1026 at 2188. Overall, the study concluded that “[o]ver 2 years, the 2.0 mg dose did not show any clinically meaningful difference in efficacy,

durability, or safety compared with the 0.5 mg ranibizumab dose.” Ex.1026 at 2190 (emphases added); *see id.*, 2182 (“At 12 months (the primary end point), the ranibizumab 2.0 mg monthly dose was not superior to the 0.5 mg monthly dose and did not offer any incremental improvements in efficacy out-comes” (emphasis added)). Similarly, a few years later, Genentech, the study sponsor of the HARBOR study, concluded that “[h]igher molar doses of anti-VEGF do not lead to greater efficacy or durability,” citing the results from the HARBOR study. Ex.2126 at 22.

189. Dr. D’Amico agreed at deposition that the HARBOR authors concluded that, over two years, the 2.0 mg dose did not show any clinically meaningful difference in efficacy, durability, or safety compared with 0.5 mg ranibizumab. Ex.2053 (D’Amico Dep. Tr.) at 392:12-393:9. Thus, primary publications, Busbee and Ho, reporting the outcomes after one year and two years of the study, respectively, both contradicted Stewart’s generalized summary and hypothesis that “increasing the dose of a drug could prolong its duration of action.” Ex.1003 ¶ 92.

190. Stewart—in characterizing the results from the ranibizumab studies as “consistent with previously published models which predict that increasing the dose ... has a greater effect on its durability than its efficacy”—cites only to Gaudreault. Ex.1039 at 1182 & n.114 (citing Ex.2014). Figure 4 of Gaudreault presents predicted concentration-effect curves for VEGF activity after ITV administration at various doses of ranibizumab (50, 500, and 2,000 µg/eye), overlaying the predicted

vitreous drug concentration (declining linearly on a logarithmic scale) with sigmoidal curves representing the predicted inhibition of VEGF activity derived from in vitro studies. Ex.2014 at 730, Fig. 4. This figure demonstrates that, at all three dose levels, ranibizumab achieves near-complete—approximately 100%—inhibition of VEGF activity shortly after administration. Ex.2014 at 730, Fig. 4. In other words, the maximum pharmacodynamic effect (full VEGF inhibition) is reached even at the lowest dose examined, and increasing the dose beyond that threshold does not produce a greater degree of VEGF inhibition. However, it is critical to distinguish this pharmacodynamic observation from the pharmacokinetic behavior of the drug. The fact that maximum VEGF inhibition is achieved at a given dose does not mean that administering a higher dose of ranibizumab would cause the drug to remain active in the body for a meaningfully longer period.

191. Gaudreault was a pre-clinical *animal* study, and a POSA would have known that pharmacokinetic (PK) toxicity studies conducted in animal models do not directly translate to humans, as there are fundamental interspecies differences in drug metabolism and clearance mechanisms. Ex.2094 at 1008. Moreover, Gaudreault also taught that increasing dose increased inflammation without any efficacy benefit. Ex.2014 at 727-728 (“absent to moderate” inflammation for 0.5 mg and “moderate to severe” inflammation for 2 mg). Although animal studies are commonly used in preclinical development to predict the metabolic behavior of new

compounds in humans, a POSA would not have understood this pre-clinical *animal* study described in Gaudreault and Stewart's commentary on Gaudreault's study as implying safety or clinical superiority or increased duration of action of an even higher 8 mg dose in humans with wet AMD or diabetic macular edema.

192. Clinical trials involving another FDA approved anti-VEGF agent, pegaptanib (Macugen®) showed that higher doses of pegaptanib not only failed to provide additional benefit, but, in some cases, were also associated with worse clinical outcomes. In the phase III V.I.S.I.O.N. trial, patients with AMD were randomized to receive intravitreal injections of pegaptanib at 0.3 mg, 1.0 mg, or 3.0 mg, or a sham injection every six weeks over 48 weeks for a total of nine doses. Ex.2088 at 2805. At the end of the study, the risk of severe vision loss (30 or more letters) was highest in the 3.0 mg group (14%) compared with the 0.3 mg group (10%) and 1.0 mg group (8%), strongly suggesting that the highest dose may be less favorable. Ex.2088 at 2810; Ex.1048 at 5. This finding was confirmed by a separate safety-pharmacokinetic trial, again finding that the efficacy of pegaptanib did not increase above the 0.3 mg dose, while adverse effects were more pronounced at higher doses. Ex.2103 at 1707-08. The Macugen® label similarly states: "Doses of Macugen up to 10 times the recommended dosage of 0.3 mg have been studied. No additional adverse events have been noted but there is decreased efficacy with doses above 1 mg." Ex.1048 at 5.

193. Dr. D’Amico also cites a 2012 Assessment Report produced by the EMA, which summarizes findings from Eylea® clinical trials, to support his opinions. Ex.1003 ¶¶ 174, 179 (citing Ex.1058). But Ex.1058 does not teach an 8 mg dose, and in fact teaches the POSA to use lower dosages in anti-VEGF formulations. Ex.1058 at 20-21.

194. Dr. D’Amico further refers to a 2011 Clinical Review from the Center for Drug Evaluation and Research. Ex.1003 ¶¶ 379-382 (citing Ex.1008). In summarizing two studies comparing 0.5, 2, and 4 mg aflibercept doses, the Clinical Review explained that “the maximum improvement [was] achieved at a dose of 2 mg/eye,” that “[t]here was little further improvement observed at 4 mg/eye,” and that “4 mg[] was not associated with improvements in the efficacy parameters beyond those achieved with a dose of 2 mg.” Ex.1008 at 10, 13. It further reported that none of the studied doses of 0.5, 2, or 4 mg “provide[d] a sustained [pharmacodynamics] improvement over the entire [twelve-week] dosing interval.” Ex.1008 at 10. With no improvement reported from 2 to 4 mg in duration or efficacy, the POSA would have been motivated against trying even higher doses of aflibercept, especially given the potential safety concerns at higher doses, such as increased inflammation and risk of Anti-Platelet Trialists Collaboration events, including cerebrovascular accidents or myocardial infarction.

195. A POSA would also have been concerned about causing inflammatory-related adverse events by increasing the dosage of aflibercept from 2 mg to 8 mg. These concerns would have been more pronounced because 2.0 mg of Eylea® was not considered a low dose. At the priority date, the sole marketed VEGF antagonist fusion protein product was Eylea®, which contains a 40 mg/ml formulation of aflibercept that delivered a 2.0 mg dose in a 50 microliter injection volume. Ex.1050 at 1; Pet. 58-59. The leading VEGF antagonist before Eylea® was ranibizumab, which was ultimately approved (1) at a maximum dose of 0.5 mg and a concentration of 10 mg/ml for wAMD, and (2) at an even lower 0.3 mg dose at a 6 mg/ml concentration for patients with diabetic macular edema. Ex.1055 at 1-3.

196. During ranibizumab pre-clinical studies, animals receiving a higher concentration formulation of ranibizumab, 40 mg/ml formulation (2 mg) exhibited “moderate to severe inflammation,” while animals receiving a low dose, 10 mg/ml ranibizumab formulation (0.5 mg) only exhibited “absent to moderate” inflammation. Ex.2014 at 727-728. Further clinical studies reinforced the risk of increasing VEGF antagonist dose. Patients in a ranibizumab clinical trial experienced dose-dependent increases in inflammation and “dose-limiting toxicity”—including, in one patient, transient vision loss—at a 1000 µg dose, which corresponds to a 20 mg/ml concentration using ranibizumab’s disclosed 50 µL volume, but not at lower doses. Ex.2018 at 1049-1052. Due to this observed dose-

dependent inflammation, the investigators did not even attempt the 2.0 mg dose corresponding to a 40 mg/ml concentration at that volume. Ex.2018 at 1049-1052.

197. Multiple companies that sought to develop higher-dose VEGF antagonist products failed. *Supra* §VII.F. Abicipar was a known VEGF antagonist in development at a 2.0 mg dose but with a much lower molecular weight, giving rise to an over threefold higher molar concentration than the aflibercept in Eylea®. Ex.2010 at 239. Yet abicipar exhibited substantial inflammation, *e.g.*, Ex.2010 at 239, and ultimately failed to obtain approval due to the “rate of intraocular inflammation observed,” which resulted in “an unfavorable benefit-risk ratio.” Ex.2008 at 1. Similarly, brolucizumab was developed to lessen treatment burden and contained a higher (6 mg) dose than Eylea® (2 mg), yet it also resulted in higher intraocular inflammation, Ex.2024 at 92; Ex.2012, leading to cases of “irreversible severe vision loss” and abandonment by ophthalmologists, Ex.2013 at A7; *see supra* §VII.F.⁴

198. Experts would also have been concerned that elevated dosages of anti-VEGF agents might heighten the risk of cardiovascular events, particularly in patients with underlying risk factors. Ex.1058 at 80. During the first AMD trial,

⁴ Of note, risks of inflammation associated with abicipar and brolucizumab and their subsequent failures were not known to a POSA until after the priority date. However, I am informed by counsel that such later failures of others could serve as objective evidence supporting non-obviousness.

aflibercept doses between 0.3 mg/kg and 3 mg/kg were administered intravenously. Ex.1039 at 6. Though patients experienced modest vision improvements and improvements in macular thickness by 66%, two of five patients receiving the highest dosage suffered dose-limiting hypertension and proteinuria. Ex.1039 at 6.

199. During this time, studies reported conflicting evidence over whether intravitreal treatment with anti-vascular endothelial growth factor (VEGF) agents increases the risk of stroke. The clinical study involving Lucentis®, the SAILOR trial, showed a dose-dependent increase in risk stroke— a 1.2% risk of stroke in the 0.5 mg arm and a 0.3% risk in the 0.3 mg arm. Ex.2102 at 1. The Lucentis® label accordingly noted a possible risk of cardiovascular events, Ex.2066 at 3, and the Diabetic Clinical Research Network published on the potential risk of cerebrovascular and cardiovascular events for patients receiving higher doses of ranibizumab (0.5 mg) for treatment of proliferative diabetic retinopathy. Ex.2143 at 673. Other meta analyses showed “an increase in stroke risk from 10.7 to 18.6 per 1000 patients annually after initiation of treatment with either intravitreal anti-VEGF agent,” and “an increased risk of hospitalization for ischemic stroke in the second month after ranibizumab treatment for wet AMD.” Ex.2102 at 1. However, other studies collecting Canadian and Medicare data “showed that the introduction of anti-VEGF agents did not increase the risk of stroke in patients with wet AMD.” Ex.2102 at 1. Even though cardiovascular events were regarded as rare when patients were

provided intravitreal administration at 2 mg, a POSA could not have ruled out the possibility of such safety issues at four-times the dosage of 8.0 mg.

200. These issues would have been particularly concerning to a POSA because studies suggested that different anti-VEGF agents may exhibit different safety profiles due to structural differences and pharmacokinetic variations, and some VEGF inhibitors may trigger fewer potential side effects than aflibercept. *E.g.*, Ex.2085 at 5. Ranibizumab is an antibody fragment lacking the Fc domain, making it much smaller than both aflibercept and bevacizumab. Ex.2085 at 5. In addition, because it lacks the Fc domain, ranibizumab also exhibits lower systemic exposure following intravitreal injection. Ex.2085 at 5. In the pharmacokinetic study, aflibercept substantially suppressed circulating plasma-free VEGF with mean levels below the lower limit of quantitation as early as three hours after administration and sometimes, up to more than seven days. In contrast, mean free VEGF levels with ranibizumab were largely unchanged. Ex.2085 at 5. A POSA would have understood these data to suggest that pharmacokinetic variations among non-specific VEGF inhibitors may represent clinically meaningful differences regarding the risk of systemic effects, such as cerebrovascular and cardiovascular events. Ex.2085 at 5.

201. A comparative study similarly found that ranibizumab may offer the “broadest safety profile” among anti-VEGF agents for retinal cells, including

aflibercept. Ex.2107 at i15. In this study, researchers directly compared the safety profiles of four anti-VEGF drugs—ranibizumab, bevacizumab, aflibercept, and ziv-aflibercept—using cultured human retinal pigment epithelial cells by exposing cells at 1/2×, 1×, 2×, and 10× clinical concentration for 24 hours. Ex.2107 at i12.

202. The study found that among the anti-VEGF drugs tested, ranibizumab best preserves the overall health of retinal pigment cells and, unlike aflibercept, that such effects may be maintained even at higher doses. Ex.2107 at i15. For instance, at 10-fold increase in the clinical concentration, all drugs except ranibizumab reduced cell viability. Ex.2107 at i11. Signs of mitochondrial damage or toxicity were observed at standard doses for bevacizumab and ziv-aflibercept, at 2× and 10× doses for aflibercept, and at 10× for ranibizumab, with no significant changes at lower doses. Ex.2107 at i11. These results would have conveyed to a POSA that multiplying standard doses can cause varying safety effects among different anti-VEGF agents at least in retinal epithelial cells, and that aflibercept, at higher doses, may lead to greater cell toxicity than comparable increases with ranibizumab.

203. None of the prior art cited by Dr. D’Amico—including the AU Label (Ex.1009), Clinical Review (Ex.1008), Stewart (Ex.1039), Nguyen 2009 (Ex.1034), Nguyen 2012 (Ex.1035), the Lehman Brother Presentation (Ex.1035), EMA Assessment Report (Ex.1058)—would have motivated the POSA to pursue an 8 mg dose of aflibercept . Nor did any of these references, combined with prior art as

whole, demonstrate that a higher dose, including an 8 mg would offer greater efficacy, longer duration of action or improved safety. On the contrary, prior art, particularly the AU Label, raised safety concerns that would have dissuaded a POSA from using a higher dose. Thus, a POSA would not have been motivated to administer an 8 mg dose of aflibercept to treat angiogenic eye disorders with a reasonable expectation of success.

X. The POSA Would Have Desired a Drug Product With an Injection Volume No Greater than Existing, FDA-Approved Intravitreal Protein Formulations

204. As of May 2018, the POSA would have desired to minimize the volume of an intravitreal injection to no greater than 50 μ L due to increased risks associated with larger volume. The vitreous cavity is a closed, fluid-filled compartment with limited capacity, Ex.1029 at 376, Fig.3. Thus, introducing additional fluid elevates intraocular pressure (IOP). *See supra* §VII.C. Larger injection volumes can cause more pronounced and sustained IOP increases. Ex.1014 at S14; Ex.1009 at 35. Both transient and acute IOP increases have been observed in patients receiving 50 μ L intravitreal anti-VEGF injections, and these events are considered more common with volumes above 50 μ L. Ex.2087 at 930-933. Given the documented risks of elevated IOP—especially in a sub-population particularly susceptible to IOP changes—a POSA would have aimed to keep the volume at 50 μ L and would not have considered volumes above 100 μ L suitable for intravitreal administration.

205. By May 2018, both transient and acute elevations of IOP following intravitreal administration of anti-VEGF agents were well-documented in the peer-reviewed medical literature. *See supra* §VII.C. For example, a study conducted in 2007 examined short-term IOP changes after intravitreal injections of bevacizumab. Ex.2123 at 807. The study found that while intravitreal injections were generally safe with respect to short-term changes, more than 10% of patients (13 out of 104 patients) experienced statistically significant IOP spikes above 50 mm Hg. Ex.2123 at 810. Such spikes can reduce capillary perfusion of the optic nerve—a critical structure transmitting visual signals from the retina to the brain—and potentially cause nerve damage. Ex.2123 at 808, 810.

206. The transient IOP elevations typically subside after 30 to 60 minutes following intravitreal administration. However, other studies have reported sustained intraocular pressure elevations following intravitreal anti-VEGF injections (ranibizumab, bevacizumab, and pegaptanib) that persist beyond the initial one-hour window. For example, a retrospective study, Choi (Ex.2124), found that 9.4% (14 out of 155 eyes) developed IOP above 25 mmHg, and 7 patients (5.5%) met the threshold for sustained elevated IOP—defined as IOP greater than 25 mmHg on at least two separate visits or any elevation requiring glaucoma medication or surgery. Ex.2124 at 1028. Another study, Tseng (Ex.2086), similarly reported sustained IOP

elevation in approximately 3.4% (19/555) to 4.5% (19/425) of patients treated with intravitreal anti-VEGF agents for neovascular AMD. Ex.2086 at 242.

207. The majority of these patients required IOP lowering medications and some even required surgical interventions. Ex.2124 at 1028; Ex.2086 at 245. In the Tseng study, among those who continued anti-VEGF treatment despite experiencing sustained IOP elevations, all eventually required some form of antiglaucoma therapy. Ex.2086 at 245.

208. A POSA would have also recognized that a subpopulation of patients receiving anti-VEGF treatments have a co-existing condition, glaucoma, making them particularly vulnerable to IOP elevations. Glaucoma, which affected approximately 60.5 million people as of 2010, is characterized by progressive optic nerve degeneration; lowering IOP remains the only proven therapeutic strategy. Ex.1015 at 4206. As such, a POSA would have understood that patients with pre-existing glaucoma are at a heightened risk for sustained IOP elevation following anti-VEGF injections. Ex.2086 at 245 (noting that the rate of sustained IOP elevations was 33% in eyes with preexisting glaucoma compared to only 3.1% in eyes without preexisting glaucoma). A POSA would have further known that for glaucoma patients, even these transient elevations in IOP can cause permanent optic nerve damage and vision loss. Ex.1014 at S7, S14.

209. A POSA would have been particularly concerned about the combined effects of higher dose and greater volume, which can potentially lead to even more frequent and pronounced IOP spikes. The earlier discussed Macugen® trial showed that higher dose, irrespective of volume, can cause elevation in IOP. *See supra* §VII.D.1. The study involved 90 µL intravitreal injections of pegaptanib (Macugen®) at three different doses: 0.3 mg, 1 mg or 3 mg. Unlike the injection volume commonly used for other anti-VEGF agents (50 µL), pegaptanib is delivered in a higher volume of 90 µL, and the study isolated the effects of doses—0.3 mg, 1 mg or 3 mg, by keeping the volume the same across all three doses. The results showed that all three doses were associated with elevated IOP: on average, IOP measured 3 to 8 mmHg higher 30 minutes after injection compared to baseline, with the largest increases observed in the 3.0 mg group. Ex.2103 at 1708. However, the proportion of patients experiencing IOP elevations to 35 mmHg or higher was 4% (2/54) in the 1.0 mg group, 21% (12/56) in the 3 mg randomized cohort, and 19% (7/37) in the 3 mg open-label cohort. Ex.2103 at 1708, 1712.e2. At these levels, there is risk of glaucomatous damage, and in patients with pre-existing optic nerve damage from glaucoma or other conditions, severe vision loss may occur. Ex.1014 at S7, S14; Ex.2085 at 3. In addition, three participants in the 3.0 mg group required a single post-injection paracentesis—a minimal, but invasive, precise eye procedure done to rapidly lower the IOP, in which an ophthalmologist creates a tiny, controlled

incision at the edge of the cornea to access and drain a small amount of fluid (aqueous humor) from the front part of the eye. Ex.2103 at 1708. A POSA would have understood that these IOP differences between doses cannot be attributed to volume because all groups received the same 90 μ L injection. Ex.2103 at 1703.

210. Because of these known risks, a POSA would have preferred a volume not exceeding 50 μ L—the standard injection volume for all intravitreal anti-VEGF protein formulations, including Eylea® (2 mg), Lucentis®, and off-label Avastin®—unless the benefits were proven to outweigh any risks in clinical trials. Ex.1055 at 1; Ex.1017 at 1898; Ex.1053 at 1. Fiedler, one of references on which Dr. D’Amico relies in Ground 2, confirms that his “most preferabl[e]” injection volume “administered to the patient is 0.05 ml,” which equates to 50 μ l. Ex.1011 at [0067]. Dr. D’Amico also agrees that 50 μ L was “certainly a target volume for intravitreal agents.” Ex.2053 (D’Amico Dep. Tr.) at 429:15-431:13 (also agreeing that Fiedler disclosed 50 microliters as a “most preferable injection volume,” that other VEGF antagonist intravitreal injections used 50-microliter volumes); *see also* Ex.1003 ¶ 292.

211. In general, a POSA would not have entertained volumes in excess of 100 μ L, especially given the known risks associated with anti-VEGF agents, the above-mentioned Macugen® trial and the sub-population of patients particularly vulnerable to IOP spikes. Ex.2103 at 1707, 1712.e.2. Dr. D’Amico appears to agree.

Ex.1003 ¶ 194 (“POSA would have further understood that 0.1 ml (or 100 µL) was considered the upper safe volume limit for a liquid formulation for intravitreal injection to the eye given the risks of increased intraocular pressure with intravitreal injections.”). He similarly testified that “high volumes are bad.” Ex.2053 (D’Amico Dep. Tr.) at 294:16-295:12.

212. But even with this “upper limit” in mind, the POSA would have had good reason to use an injection volume of 50 microliters—the amount that had already been tested and tried over millions of injections worldwide without causing substantial intraocular pressure issues. Concerns over larger injection volumes up to and including 100 microliters remained unresolved even after May 2018, as evidenced by apprehension over intraocular pressure spikes associated with a clinical molecule, lampalizumab. Lampalizumab was developed as a potential treatment for geographic atrophy (“GA”), the most advanced form of age-related macular degeneration. Ex.2095 at 667. It was administered at 100 µL, and many clinicians raised concern that such a large volume could lead to spikes in intraocular pressure. Ex.2095 at 671 (“Increases in intraocular pressure (IOP) were of interest because lampalizumab was injected as 0.1 mL, twice the volume of most intravitreal injections of anti-VEGF.”). At the conclusion of the clinical trial, I authored an article documenting and summarizing “intraocular pressure outcomes after lampalizumab injections,” because safety of “repeated doses of intravitreal

lampalizumab”—administered in “0.1 mL, twice the volume used for anti-VEGF intravitreal injections”—had not been established. Ex.2096 at E2. I believed that “[t]his information could help inform future clinical trial design as well as support safety evaluations of more recently approved intravitreal injections that use volumes of 0.07 to 0.1 mL,” Ex.2096 at E5. I understand that Ex.2095 and Ex.2096 were not published before May 2018, and thus would not have been available to the POSA as prior art. However, Ex.2095, published in June 2018, reflects the prevailing concerns that existed as of May 2018. Both documents reflect that concerns regarding a 100 µL injection volume existed and persisted beyond the priority date.

213. Dr. D’Amico testified that a POSA would not have considered volumes that are not increments of 10 µL because “syringes are only graded in [10 µL] .7, .8, .9,” and “syringes are not marked in finer gradations than [10 µL].” Ex.2053 (D’Amico Dep. Tr.) at 297:7-20; 297:21-299:1. I respectfully disagree. While I acknowledge that syringes are commonly graded in 10 µL increments, Dr. D’Amico overlooks the fact that drugs are often provided in pre-filled syringes, where the volume is not constrained by the syringe gradations. A pre-filled syringe is supplied by the manufacturer already containing a measured dose of the drug, ready to be administered to a patient. Ex.1011 at [0042]. A clinician need not draw the drug from the vial using an empty syringe. Ex.1011 at [0042]. Fiedler explains that one

of the main benefits of the pre-filled syringe is “greater dose precision”—“pre-measured dosage reduc[es] dosing errors due to the need to reconstitute and/or draw medication into a syringe.” Ex.1011 at [0007]. In fact, both Lucentis® and Eylea® are available in pre-filled syringes. Ex.1055 (Lucentis® Label) at 8; Ex.1009 (Eylea® Label) at 35. Thus, I disagree with Dr. D’Amico that a POSA’s selection of volume would be limited to 10 µL increments.

214. For the reasons I have explained, when considering the injection volume of a drug product, the POSA would not have desired a drug product with an injection volume less than 50 µL, would have considered 100 µL as the upper limit for intravitreal injection volume, and would have considered the full range, not restricted by 10 µL gradations on a syringe.

XI. The POSA Would Have Desired a Drug Product With Viscosity Comparable to Existing, FDA-Approved Intravitreal Protein Formulations

215. High-viscosity drugs are perceived as being more difficult to administer intravitreally, increasing the likelihood of injection-related adverse events. Higher viscosity drugs require increased injection force to administer, particularly when using the fine-gauge needles suitable for intravitreal injections. Ex.2115 at 352. From a clinician’s perspective, this means that a highly viscous intravitreal drug formulation can require greater finger pressure, make the plunger movement less smooth and predictable, increase injection time, and/or reduce the clinician’s ability

to deliver the dose in a controlled, steady manner while the needle is positioned in the eye. *See* Ex. 2116 at 604; Ex.1010 at [0007]. For the experienced ophthalmologist giving intravitreal injections, the ability to delicately control the injection matters because the patient is awake and aware that a needle is in the eye, and an uneven plunger movement or longer injection times can be a source of distress and anxiety.

216. High viscosity also creates a syringe-needle connection concern. When more force is needed to expel the drug, more pressure is transmitted through the syringe and needle assembly, including at the needle hub. Ex. 2116 at 604, 608. This pressure, in turn, may increase the risk of hub loosening, leakage, or even needle dislodgement. This risk is especially concerning when using a Luer slip syringe, where the needle is pushed onto the syringe tip and held by friction, as compared to a Luer lock syringe, which uses a threaded tip, requiring a needle or its attachment to be pushed and twisted into place, wherein the screw-on mechanism prevents the needle from popping off under pressure.

217. In my opinion, a POSA would not have wanted to use a larger needle than the typical 30-gauge needle. Larger needles (which, counterintuitively, are denoted by a lower gauge number) have a larger outer diameter, which increases the risk of complications unique to the intravitreal route of administration. Ex.1024 at 789; Ex. 1001 at 13:33-36.

218. The eye is a small, enclosed, and delicate organ, and insertion of a larger-diameter needle through the sclera and into the vitreous cavity increases the likelihood of discomfort or reflux of the medication injected into the vitreous cavity. Ex.1024 at 788-790; Ex.1015 at 4207. A larger-bore needle also leads to an increased likelihood of content from the vitreous cavity to reflux through the scleral injection site, which can reduce the effective dose of medication delivered into the vitreous cavity. Ex.2120 at 1403 (finding a significantly higher incidence of postinjection vitreous reflux in eyes injected with larger 30-gauge needles (53%) than in eyes injected with smaller 32-gauge needles (13%)); Ex.2121 at 240-41 (observing in porcine and bovine eye models that reflux occurred less often as needle gauge increased, with larger 27-gauge needles producing more and darker reflux than 30- or 31-gauge needles).

219. Conversely, from my experience, needles finer than 30 gauge often lack the tensile strength to penetrate the eye easily. There is also a report that needles smaller than 30 gauge may in turn lead to an increase in reflux, probably due to the lack of intravitreal space available for very small needles and a stronger counteracting force. Ex.2121 at 241; Ex.2122 at 171 (finding that 32-gauge needles produced more reflux than 30-gauge needles, likely due to the smaller intravitreal space created by the narrower needle and greater pressure at the wound site). For these reasons, the clinical standard in ophthalmology has consistently favored 30-

gauge or finer needles for intravitreal injections. Ex.1014 at S13; *see also supra* §VII.C.

220. Along these lines, Dr. D’Amico testified that “[h]igh viscosities are bad,” and that an acceptable formulation must pass through a 30-gauge needle at an appropriate volume and viscosity. Ex.2053 (D’Amico Dep. Tr.) at 294:16-296:19. “[I]f the formulator ‘makes tar,’ he testified, ‘it’s no good to me.’” Ex.2053 (D’Amico Dep. Tr.) at 294:16-296:19. Dr. D’Amico also testified that a more viscous formulation would require a larger needle bore to force it through the needle into the eye. Ex. 2053 (D’Amico Dep. Tr.) at 420:13-421:12. For the reasons I have explained, the POSA would not have wanted to increase the size of the intravitreal injection needle.

XII. The POSA Would Not Have Understood Larson to Teach Intravitreal Formulations or Follow Its Teachings to Reduce Viscosity by Adding Dyes

221. Dr. D’Amico relies on the Larson reference and suggests that Larson taught “[p]referred needle gauges for the delivery of the low-viscosity formulations include 27, 29, and 31 gauge, optionally thin walled.” Ex.1003 ¶ 183 (quoting Ex.1010 at [0079]). Dr. D’Amico further states that “[t]hese needle sizes are consistent with those disclosed in Vitti and the AU Eylea® Label—as well as those used for commercially available intravitreally (i.e., ranibizumab (Lucentis®).” Ex.1003 ¶ 183. None of those references—nor the labeling for Eylea® or

Lucentis®—specifies a needle with a gauge lower than 30 for intravitreal use. To the contrary, each specifies a 30-gauge needle. Ex.1007 at [0127] (“In one embodiment, the Syringe is a 2 mL long glass syringe fitted with a 30-gauge thin wall needle”); Ex.1009 at 31, 34 (“For the intravitreal injection a 30 G x ½ inch injection needle should be used.”); Ex.1055 (Lucentis® label) at 3 (“For the intravitreal injection, a 30-gauge x ½ inch sterile injection needle should be used (not provided).”).

222. I have reviewed Larson from the perspective of a clinician. In my opinion, the reason Larson mentions needle gauges lower than 30 (*i.e.*, 27 and 29, which correspond to larger-diameter needles) is that Larson is not primarily directed to intravitreal administration, but other routes of delivery, including subcutaneous and intramuscular injection, where larger-diameter needles are both common and clinically acceptable. *See, e.g.*, Ex.1010 at Abstract (“Concentrated, low-viscosity, low-volume liquid pharmaceutical formulations of proteins have been developed. Such formulations can be rapidly and conveniently administered ***by subcutaneous or intramuscular injection***, rather than by lengthy intravenous infusion.”); Ex.1010 at ¶ 21 (nearly identical); Ex.1010 at ¶ 74 (stating that “low-viscosity protein solutions” can be “useful for ***subcutaneous (SC) and intramuscular (IM) injections***”); Ex.1010 at ¶ 224 (describing administration “by ***intramuscular,***

intraperitoneal (i.e., into a body cavity), intracerebrospinal, or subcutaneous injection”) (emphases added).

223. Although, for the reasons I describe above, the POSA would have been concerned about increased viscosity when increasing the aflibercept dosage, the POSA would not have adopted Larson’s approach of adding organic dyes to adjust viscosity without safety evidence for their use in intravitreal administration. Multiple studies have found that organic dyes injected into the vitreous cavity to stain the retinal surface carry risks of toxicity and loss of visual acuity. D’Amico asserts that “[a] POSA would have been informed by the broad teachings in Larson of a target viscosity for injecting high-concentration protein formulations through the small needles required for intravitreal administration.” Ex.1003 at ¶ 185.

224. However, Larson does not address the formulation of fusion proteins or the viscosity of proteins intended for intravitreal administration. Larson, a patent application, is directed generally to “liquid protein formulations containing water soluble organic dye,” Ex.1010 at 1, but is not directed to any specific protein and mentions hundreds of proteins to which its disclosed formulations may be applicable. Ex. 1010 at [92-190]. While these include fusion proteins, Larson mentions Eylea® as just one of over thirty examples. Ex. 1010 at [164-81].

225. Moreover, Larson is directed to other types of administration, including subcutaneous and intramuscular. Ex. 1010 at [75]. Larson’s sole mention of

“intravitreal” appears in a passing reference to Eylea® among a list of over 700 biological products. *E.g.*, Ex. 1010 at [88-190]. During his deposition, Dr. Falconer admitted that Larson is “generally directed to achieving viscosity suitable for subcutaneous and intramuscular injection,” and that the viscosity passages he relied on refer to SC/IM injections with “no reference” to intravitreal injections. Ex.2046 (Falconer Tr.), 118:25-119:2, 134:1-5. He likewise admitted that Larson’s working examples are aqueous solutions of therapeutic monoclonal antibodies, not intravitreal formulations, and ultimately agreed that Larson “does not disclose any formulations suitable for intravitreal administration.” Ex.2046 (Falconer Tr.) at 137:12-17. Therefore, Larson’s subcutaneous or intramuscular focused disclosure cannot supply the missing teaching that a fusion-protein formulation would have a viscosity suitable for intravitreal administration.

226. Dr. D’Amico further asserts that “Larson taught one way ‘to provide low-viscosity liquid formulations of pharmaceutically important proteins, especially high-molecular-weight proteins, such as mAbs.’” Ex.1003 at ¶185. While I agree that Larson describes “one way” for producing low-viscosity liquid formulations, I disagree that this approach would be suitable for formulating aflibercept, a protein administered directly into the eye via injection. Larson discloses a technique to potentially decrease viscosity by formulating therapeutic protein formulations with “viscosity-lowering water soluble organic dyes.” Ex. 1010 at [23]. Larson also

notes that “[i]n the absence of a viscosity-lowering water soluble dye, the viscosity of a protein formulation increases exponentially as the concentration is increased.” Ex. 1010 at [75].

227. However, because the safety profiles of most organic dyes are largely unknown, and the FDA requires a rigorous evaluation and approval process before any new inactive drug ingredient may be used in a pharmaceutical product, a POSA could not have used water-soluble organic dyes to lower the viscosity of a drug intended for intravitreal administration with a reasonable expectation of success. Dr. D’Amico admitted that he did not offer an opinion on whether a POSA developing an intravitreal formulation would have considered adding the dyes described in Larson. Ex.2053 at 425:19-426:7. He also could not identify any anti-VEGF intravitreal formulation that contains a dye. Ex.2053 at 426:20-427:14.

228. For instance, none of the organic dyes listed in Larson appear on the FDA’s list of “Color Additives Approved for Use in Drugs,” 21 C.F.R. § 74, and the FDA requires that any new excipient—defined as an “inactive ingredient intentionally added to a therapeutic . . . product”—undergo a separate and independent approval process before it may be incorporated into a drug formulation, *see* Ex. 2112 at 1, 2-8. And a POSA would have known that such approval process is both lengthy and demanding. For example, the FDA guidance (Ex.2112) states, “[i]t is important that a new or inadequately qualified inactive ingredient proposed

for use in any product to be marketed pursuant to an NDA, biologics license application (BLA), or ANDA be supported by adequate data.” Ex. 2112 at 3. It also recommends safety pharmacology studies, pharmacokinetic testing, chronic six-month repeat-dose toxicology studies, genotoxicity testing, reproductive toxicology studies, and carcinogenicity assessment prior to using a new inactive ingredient in a pharmaceutical drug. Ex. 2112 at 4-7.

229. Moreover, at least some of the organic dyes mentioned by name in Larson are known to be toxic to the eyes and to retinal cells, further underscoring that a POSA would not have turned to such dyes with any reasonable expectation of success. For example, Congo Red is known to cause chemical conjunctivitis and corneal damage. Ex.1010 at [213]; Ex.2097 at 3-5; Ex.2098 at 4-7. Amaranth is associated with eye irritation. Ex.1010 at [213]; Ex.2099 at 1. Light Green SF Yellowish and other commonly used dyes have demonstrated intravitreal toxicity and retinal cell toxicity, as well as eye irritation. Ex.1010 at [213]; *see also* Ex.2100 at 497. Crystal Violet is known to cause eye damage. Ex.1010 at [213]; Ex.2101 at 1. A POSA, aware of these known toxicities, would have had no reason to believe that organic dyes such as those disclosed in Larson could be safely administered via intravitreal injection.

XIII. The POSA Would Not Have Understood Eylea Clinical Review to Teach IVT Administration of Aflibercept to Not Cause a Significant Increase in Blood Pressure.

230. The 2011 Eylea Clinical Review (“Clinical Review”) summarized the results of Phase I and Phase II clinical trials of aflibercept administered both intravenously and intravitreally. Ex.1008 at 2. Dr. D’Amico relies on the Clinical Review solely for the disclosure that patients receiving aflibercept would not experience a significant increase in blood pressure, Ex.1003 ¶¶ 379-381, and that “[a] POSA would reasonably expect the lack of a significant increase in blood pressure after intravitreal administration of low dose Eylea® to also be the case for intravitreal injection of higher concentrations, 8 mg aflibercept[,]” Ex.1003 ¶ 382.

231. The Clinical Review explains that both diastolic blood pressure and systolic blood pressure increase after intravenous administration of a VEGF antagonist because the administration reduces the amount of free systemic VEGF. Ex.1008 at 11. These blood pressure effects were not found after the lower-concentration intravitreal injections, which were performed at concentrations up to 4 mg/eye. Ex.1008 at 11. Notably, the Clinical Review did not evaluate the safety of administering a higher, 8 mg dose of aflibercept. As Dr. D’Amico acknowledged, toxicity of drugs can depend on peak concentration, and “a higher dose yields a higher peak concentration.” Ex.2053 at 100:14-101:15. The Clinical Review does not provide enough data for a POSA to reasonably expect that an intravitreal

injection of a higher dose would produce the same clinical effects as a lower dose. In other words, absent additional clinical data, a POSA could not reasonably expect that patients would not experience a significant increase in blood pressure after intravitreal administration of a higher dose, an 8 mg aflibercept.

XIV. My Opinions Regarding Obviousness

232. As I explained above, I understand Alvotech to assert that the following claims would have been obvious to the POSA as of May 2018 in view of the following combinations of alleged prior art:

Ground	Claims	Alvotech's Combination of References
1	1, 4-38	Vitti, AU Eylea® Label, and Larson
2	1, 4-38	Vitti, AU Eylea® Label, and Larson
4	2, 3	Larson, Vitti, AU Eylea® Label, and 2011 Eylea® Clinical Review
5	2, 3	Furfine, Dix, Fiedler, AU Eylea® Label, Larson and 2011 Eylea® Clinical Review

233. Every challenged claim of the '036 patent recites a method for treating an angiogenic eye disorder comprising administering a dose of at least about 8 mg aflibercept. For all the reasons I explained above, it is my opinion that the POSA would *not* have been motivated to perform such a method, nor would the POSA have had a reasonable expectation of success in doing so. Accordingly, it is my opinion

that the challenged claims would not have been obvious to the POSA as of May 2018 in view of the prior art relied upon by Alvotech.

XV. Conclusion

234. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on June 19, 2026

Signature: Neil Bressler

Curriculum Vitae - SUMMARY Pages - Neil M. Bressler, M.D.

Title: The James P. Gills (inaugural) Professor of Ophthalmology – Johns Hopkins University School of Medicine; Past Chief (2005-2018), Retina Division – The Wilmer Eye Institute – Johns Hopkins Hospital

Peer-Reviewed Publications: 500

Major Research Interests: Design and implement clinical trials evaluating retinal diseases.

- Previously, Chair and Principal Investigator of numerous multicenter randomized clinical trials including over 20 sponsored by the National Eye Institute of the National Institutes of Health and several by industry, including Chair of the Diabetic Retinopathy Clinical Research Network 2006 to 2012.
- Past Network Chair of the Diabetic Retinopathy Clinical Research Network (DRCR.net) 2013 - 2019 (Network Chair: 2006-2012), involving over 25 randomized clinical trials and observation studies with over 100 community-based and university-based and community-based sites, sponsored by the National Institutes of Health.

Educational Roles:

- Fellowship, residency, and medical student programs in retina at Johns Hopkins University
- Director: Numerous annual Continuing Medical Education Courses from Johns Hopkins University

Administrative Role:

- Past Chief, Retina Division, (Chief: 2005-2018) Wilmer Eye Institute, Department of Ophthalmology, Johns Hopkins University School of Medicine (18 full-time retina physicians; additional basic science faculty; over 50 clinical staff; over 40 research staff)
- Past Chair, Dean's Committee on Outside Interests (including management of financial conflicts of interest)
- Past Chair, School of Medicine Continuing Medical Education Advisory Board

Clinical Practice: National and international referral for retinal diseases

Current Editorial Boards: *JAMA Ophthalmology* (Editor in Chief); *The JAMA Network* (Editorial Board)

Current and Past Major National Advisory Roles:

- Chair, Data and Safety Monitoring Committee, National Eye Institute Intramural Program of NIH (2003 – 2026; Chair 2006 – 2026). Current appointment: November 1, 2021 through October 31, 2026
- Ophthalmic Devices Panel of the Medical Devices Advisory Committee to the FDA (2000 – 2029; Chair, 2008-2011; 2019-2022). Current appointment: November 1, 2024 through October 31, 2029
- Observational Study Monitoring Board: Epidemiology of Diabetes Interventions & Complications (EDIC); 2011 - 2022
- Past President – Macula Society

Selected Honors:

- 1975-78: Class Honors University of Michigan
- 1978: Angell Scholar University of Michigan
- 1978: Bachelor of Science with High Distinction and Honors in Zoology
- 1978: Phi Beta Kappa
- 1982: Paul Ehrlich Award in Clinical Investigation Johns Hopkins Medical School
- 1986: Heed Fellowship
- 1987: Heed/Knapp Fellowship
- 1993: American Academy of Ophthalmology Honor Award
- 1995: Research to Prevent Blindness Olga Keith Weiss Scholars Award
- 1997: The Macula Society Rosenthal Award and Lecture
- 1999: The Society of Heed Fellows Award
- 2000: Inaugural Recipient of the Neil R. Miller Medical Student Teaching Award
- 2000: Inaugural Recipient of the James P. Gills Professorship of Ophthalmology
- 2000: National Society of Southern Dames Award
- 2001: The Alvaro Rodriguez Gonzalez Lecture and Gold Medal
- 2001: Saudi Ophthalmology Society Medal

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- 2003: The Macula Society J. Donald M. Gass Medal
- 2003: Neil R. Miller Medical Student Teaching Award
- 2003: American Society of Retinal Specialists Honor Award
- 2004: Helen Keller Foundation Award and Lecture
- 2004: The Macula Society Research and Education Award
- 2004: The American Academy of Ophthalmology's Senior Achievement Award
- 2008: The American Academy of Ophthalmology's Secretariat Award
- 2008: The American Society of Retina Specialists Gertrude Pyron Award
- 2008: American Academy of Ophthalmology Secretariat Award
- 2009: Healthnetwork Foundation Service Excellence Awards
- 2009: Silver Fellow in the ARVO Fellows Class of 2009
- 2010: Gold Fellow in the ARVO Fellows Class of 2010
- 2011: Research to Prevent Blindness Senior Scientific Investigator Award
- 2014: American Academy of Ophthalmology Life Achievement Honor Award
- 2017: Inaugural International Award and Lecture: Asia Pacific Vitreoretinal Society
- 2017: Macula Society Patz Award and American Academy of Ophthalmology Patz Lecture
- 2018: The American Academy of Ophthalmology's Secretariat Award
- 2019: Asia Pacific Academy of Ophthalmology Achievement Award
- 2019: Power List 100 Top Ophthalmologists
- 2021: Healthnetwork Foundation Service Excellence Award
- 2023: Asia Pacific VitreoRetinal Society Inaugural Dennis Lam Award and Lecture
- 2024: EyeCon Inaugural Selection by Asia Pacific Academy of Ophthalmology
- 2024: Harrell Pierce Teaching Award – Department of Ophthalmology – Johns Hopkins University
- 2025: Power List 100 Top Ophthalmologists
- 2026: Award of Merit in Retina Research and Charles L. Schepens Lecture – Retina Society

Google Scholar Metrics (as of June 15, 2026):

- Publications: 500: Dr. Bressler has 500 publications in the peer-reviewed medical literature.
- Citations: 72,546: Dr. Bressler's 500 publications have been cited in the peer-reviewed literature 71,344 times.
- h-index: 132: To quantify productivity and citation impact, Dr Bressler has at least 131 publications cited at least 132 times.
- i10-index: 379: i10-index, a Google Scholar metric, indicates that 379 of Dr. Bressler's 500 publications have been cited at least 10 times in the peer-reviewed medical literature.

BIOGRAPHICAL INFORMATION

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EDUCATION

Undergraduate: University of Michigan, Ann Arbor, MI - Bachelor of Science - 1978

Medical School: The Johns Hopkins University School of Medicine, Baltimore, MD - 1982

Internship/Internal Medicine Fellowship: Johns Hopkins Hospital - Department of Medicine - 1982-1983

Ophthalmology Residency: Harvard Medical School and Massachusetts Eye and Ear Infirmary, Boston, MA - 1983-1986

Retinal Fellowship: Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, MD - 1986-1987

ACADEMIC APPOINTMENTS

July 1, 1987 – June 30, 1988: Harvard Medical School, Department of Ophthalmology, Instructor of Ophthalmology

July 1, 1988 – October 1991: Johns Hopkins University School of Medicine, Department of Ophthalmology, Assistant Professor of Ophthalmology

October 1991 – June 1997: Johns Hopkins University School of Medicine, Department of Ophthalmology, Associate Professor of Ophthalmology

July 1997 – Present: Johns Hopkins University School of Medicine, Department of Ophthalmology, Professor of Ophthalmology

April 2000 – Present: Johns Hopkins University School of Medicine, Department of Ophthalmology, The James P. Gills Professor of Ophthalmology (inaugural recipient)

EDITOR IN CHIEF APPOINTMENTS

July 2012 – Present: Editor-in-Chief, *JAMA Ophthalmology*

PRIMARY HOSPITAL APPOINTMENTS

July 1, 1987 – June 30, 1988: Massachusetts Eye and Ear Infirmary, Assistant in Ophthalmology

July 1, 1988 – October, 1991: Johns Hopkins Hospital, Assistant Professor of Ophthalmology

October 1991 – June 1997: Johns Hopkins Hospital, Department of Ophthalmology, Associate Professor of Ophthalmology

June 1997 – Present: Johns Hopkins Hospital, Department of Ophthalmology, Professor of Ophthalmology

BOARD CERTIFICATIONS

Ophthalmology - October 27, 1987

HONORS

1975-78: Class Honors - University of Michigan
1978: Angell Scholar - University of Michigan
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2008:	American Academy of Ophthalmology Secretariat Award
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2019:	Asia Pacific Academy of Ophthalmology Achievement Award
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2024:	EyeCon Inaugural Selection by Asia Pacific Academy of Ophthalmology
2024:	Harrell Pierce Teaching Award: Johns Hopkins University
2025:	Power List 100 Top Ophthalmologists
2026:	Award of Merit in Retina Research and Charles L. Schepens Lecture – Retina Society

PATENTS

Neil Bressler, Owings Mills, MD US

Patent application number	Description	Published
20110242306	<u>SYSTEM AND METHOD FOR AUTOMATED DETECTION OF AGE RELATED MACULAR DEGENERATION AND OTHER RETINAL ABNORMALITIES</u> - A system and method for automated detection of age related macular degeneration and other retinal abnormalities which may have a retinal scanner capable of obtaining retinal data from a subject. The retinal scanner may be coupled to a central processing unit (CPU) which may have memory storing CPU-executable instructions which may detect retinal abnormalities. When the CPU receives retinal data from the retinal scanner, the system may perform CPU-executable instructions for detecting retinal abnormalities. The system may analyze the retinal data to determine one or more healthy areas and, based on the analyzed healthy area, the system may detect abnormalities in the retinal data.	10-06-2011

PEER-REVIEWED PUBLICATIONS

Google Scholar Metrics:

- Publications: 498: Dr. Bressler has 498 publications in the peer-reviewed medical literature.
- Citations: 69,632: Dr. Bressler's 498 publications have been cited in the peer-reviewed literature 69,632 times.

- h-index: 130: To quantify productivity and citation impact, Dr Bressler has at least 130 publications cited at least 130 times.
 - i10-index: 372: i10-index, a Google Scholar metric, indicates that 372 of Dr. Bressler's 498 publications have been cited at least 10 times in the peer-reviewed medical literature.
1. Bressler NM, Broekman MJ, Marcus AJ. Concurrent studies of oxygen consumption and aggregation in stimulated human platelets. *Blood* 1979;53:167-78.
 2. Bressler SB, Bressler NM, Fine SL et al. Natural course of choroidal neovascular membranes within the foveal avascular zone in senile macular degeneration. *Am J Ophthalmol* 1982;93:157-63.
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500. Bressler NM. JAMA Ophthalmology – The Year in Review, 2025: Initiatives Hitting Their Stride. *JAMA Ophthalmol* (Published on line: March 19, 2026).

TEXTBOOKS

Bressler NM, Brown GC, Flynn HW, Marmor MF, Anderson LS, Grand MG. American Academy of Ophthalmology's Basic Clinical Skills Course Section 12: Retina and Vitreous, 1996-1997, 1996.

BOOK CHAPTERS

1. Bressler NM, Bressler SB, Berson FG: Ophthalmic agents. In Manual of Drug Therapy. Eds. Steinberg DA, Scheinberg LC. New York: Raven Press, 1985.
2. Bressler SB, Bressler NM, Murphy RP: Argon laser treatment: randomized clinical trials--short and long term results. In Ocular Circulation and Neovascularization. Eds BenEzra D, Ryan SJ. Boston: Martinus Nijhoff Publishers, 1987.
3. Bressler NM, Bressler SB, Murphy RP, Fine SL: Recurrent choroidal neovascularization following successful photocoagulation in age-related macular degeneration. In Ocular Circulation and Neovascularization. Eds BenEzra D, Ryan SJ. Boston: Martinus Nijhoff Publishers, 1987.
4. Bressler NM, Bressler SB, Murphy RP, Fine SL: Recurrent choroidal neovascularization following successful photocoagulation in age-related macular degeneration. In Laser Photocoagulation of Retinal Disease. Eds Gitter KA, Schatz H, Yannuzzi LA, McDonald HR. San Francisco: Pacific Medical Press, 1988.
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7. Bressler NM, Bressler SB, Fine SL: Angiographic interpretation of classic and occult choroidal neovascularization. In Medical and Surgical Retina: Advances, Controversies and Management. Eds Lewis H, Ryan S. St. Louis: Mosby Year Book, 1992.
8. Bressler NM: Macular degeneration and related disorders. In Practical Atlas of Retinal Disease and Therapy. Ed. Freeman WR. New York: Raven Press, 1992.
9. Bressler SB, Gragoudas ES, Bressler NM: Age related macular degeneration, Part 1: Drusen and Geographic Atrophy. In Principles and Practice of Ophthalmology. Eds Albert DM, Jakobiec FA, WB Saunders Co, 1993.
10. Bressler NM, Gragoudas ES, Bressler SB: Age related macular degeneration, Part 2: RPE Detachment and Subretinal neovascularization. In Principles and Practice of Ophthalmology. Eds Albert DM, Jakobiec FA, WB Saunders Co, 1993.

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13. Neely KA, Bressler NM, Bressler SB: Epidemiology, clinical characteristics, and natural history of age-related macular degeneration. In Ophthalmology Clinics of North America: Macular Diseases. Eds., Grossniklaus HE, Kincaid MC. WB Saunders Co, 1993.
14. Bressler NM: Subretinal neovascular membrane. Master Techniques in Ophthalmic Surgery. Ed., Roy FH. Williams and Wilkins, 1995.
15. Bressler NM: Macular degeneration and related disorders. In Practical Atlas of Retinal Disease and Therapy 2nd edition. Ed. Freeman WR. New York: Raven Press, 1997.
16. Fekrat S, Bressler NM: Age Related Maculopathy. Easty and Sparrow: Oxford Textbook of Ophthalmology, Oxford University Press 1999.
17. Rosberger DF, Bressler NM, Bressler SB: Ophthalmic Surgery: Photocoagulation. Rob & Smith's Operative Surgery, Eds., Carter DC, Russell RCG, Pitt HA, Dudley H, Lee G, Remes P, Stockman L, Ramage D. Chapman & Hall, 1998.
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22. Bressler SB, Gragoudas ES, Bressler NM: Age-related macular degeneration, Part 1: Drusen and Geographic Atrophy. In Principles and Practice of Ophthalmology, 2nd Edition. Eds Albert DM, Jakobiec FA, WB Saunders Co, 1999.

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27. Chen CJ, Bressler NM. Neovascular age-related macular degeneration: rationale for current treatment guidelines. *Ophthalmology and the ageing society*, 2013. 107-125.

EDITORIAL ROLES

Editor in Chief *JAMA Ophthalmology* 2013 to present
Editorial Board *The JAMA Network Editorial Board* 2013 to present

Completed Editorial Boards:

1991-1994: Section Editor (Reviews in Medicine), *Survey of Ophthalmology*
1995-2000: *The Wilmer Retina Update*, Editor-in-Chief (and Founding Editor)
1994-2013: Editorial Board: *JAMA Ophthalmology (formerly Archives of Ophthalmology until December 2012, and Past Editor of Controversies Section)*
1995-2013: Editorial Board: *RETINA*
2012-2013: Editorial Board: *RETINA Cases and Brief Reports*

NATIONAL ADVISORY ROLES

Current

- **Chair**, Data and Safety Monitoring Committee, National Eye Institute (NEI) Intramural Program of National Institutes of Health: 2003 – 2026; **Chair**: 2006 - 2026
- **EDIC Observational Study Monitoring Board (OSMB)** for the Epidemiology of Diabetes Interventions and Complications (EDIC) Study, National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK): 2011 – 2022

Past

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- **Chair**, Ophthalmic Devices Panel of the Medical Devices Advisory Committee for the Center for Devices and Radiologic Health, Food and Drug Administration: (Terms: 2000 – 2024; Chair Terms: 2008 – 2010; 2019 – 2024)
- **Scientific Advisor**: NEI Research for Macular Degeneration: February 1990 - December 1990.
- **Consultant** - American Academy of Ophthalmology Preferred Practice Pattern for Macular Degeneration – 1990 to 1994
- **Editor** - Basic and Clinical Science Course - Retina Section - American Academy of Ophthalmology - 1994-1998
- **Scientific Advisor** - American Federation of Aging Research - 1992-1997
- **National Eye Institute (NEI) Special Emphasis Panel Review Committee** – member: 1997, 1998, 2001, 2003
- **U.S. Pharmacopeia Expert Committee** - Member, 2000 – 2005, 2005 – 2010
- **Carotene in Age-Related Eye Disease Study (CAREDS) Scientific Advisory Board** for National Eye Institute: 2002 – 2010
- **SCORE Advisory Group Member** – National Eye Institute: 2003 – 2008
- **Testimony before U.S. House of Representatives subcommittees, Senate subcommittees**, as well as staffers for U.S. House or U.S. Senate – various years from 2008 through 2017

PROFESSIONAL SOCIETIES AND SERVICE TO PROFESSIONAL SOCIETIES

1981-2020 **Association for Research in Vision and Ophthalmology**
1995-1998 Program Committee (Chairman of Program Committee in 1998)
1998-2002 Exhibits Committee (Chairman 2002)

1987-2020 **American Medical Association**

1987-2020 **American Academy of Ophthalmology**
1994-1997 Editor, Basic and Clinical Science Course: *Retina Section*
1990-2004 Consultant, Preferred Practice Patterns
2003-2005 Committee on Aging

1990-2020 **Macula Society**
1996-2002 Member, *Executive Committee*
1996-2002 Chairman, *Program Committee*
1994-1997 Member, *Research Committee*
2008-2012 Macula Society Representative to American Academy of Ophthalmology Council
2011-2012 Officer, Secretary
2012-2013 Officer, President-elect
2013-2014 Officer, President
2014-2015 Office, Past President

1993-2020 **Retina Society**

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1997-2020 **Society for Clinical Trials**
1998-2002 Member, *Development Committee*

1998-2020 **Club Jules Gonin**

1998-2020 **American Society of Retina Specialists**
2005 Chair, *Ad hoc* Leadership Committee
2012 Co-chair, Vision 20/20
2012 Founding editor: Retina Image Bank

CLINICAL ACTIVITIES

National and international referral practice specializing in the management of medical retinal disease (e.g., diabetic retinopathy, age-related macular degeneration, retinal vein occlusions), with specific reference to treatments for these conditions as well as designing and directing clinical trials evaluating new managements of these diseases.

ADMINISTRATIVE RESPONSIBILITIES

UNIVERSITY SCHOOL OF MEDICINE ACTIVITIES

- Associate Professor Promotions Committee (1994 - 1998)
- Dean's Committee on Outside Interests (2002 – 2011; Chair 2006 – 2011)
- Continuing Medical Education Advisory Board 2010 – Present (Chair: 2014 – 2015)

DEPARTMENTAL ACTIVITIES

- Clinical Practice Advisory Committee (1989 – 2018)
- Chair, Subcommittee on Electronic Patient Record for Wilmer Institute (1995 – 1997)
- Resident Education Committee: Serve in an advisory role to the Chief Resident to identify educational needs of the residency program, including the core curriculum. (1993 – 1997)
- Chair, Wilmer Imaging Committee (2001 – 2003)

DIVISIONAL ACTIVITIES

- **Retina Division (Chief: 2005 – 2018):** One of the largest university-based retina divisions in the world; during tenure: up to 19 full-time clinical faculty (including 7 endowed professorships) with additional basic science faculty reporting to the clinical faculty with over 40,000 visits at Johns Hopkins Hospital and 5 satellite locations
- Head of Retinal Fellowship Program (1989 to 2007).
- Participation in training of over 190 residents and 140 retina fellows and numerous additional medical students and clinical research fellows.

OTHER OUTSIDE ACTIVITIES

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Board of Trustees, Interlochen Center for the Arts, Interlochen, Michigan – 2007 to 2015.

Vice-Chair: 2013 – 2015.

Lifetime Trustee (12th Life Trustee in the over 90-year history of Interlochen): 2015 to present.

Board of Directors: JAEB Center for Health Research Foundation, Inc. and JAEB Center Research Trust, Inc., a freestanding, nonprofit coordinating center for multi-center clinical trials and epidemiologic research: 2022 to present.

APPENDIX B: MATERIALS RELIED UPON¹

Paper or Exhibit Number	Description
Paper 02	Alvotech PGR Petition
Ex.1001	U.S. Patent No. 12,168,036 (Graham et al.)
Ex.1003	Declaration of Dr. Donald Joseph D’Amico
Ex.1004	Declaration of Dr. Robert J. Falconer
Ex.1005	U.S. Patent No. 7,608,261 (Furfine)
Ex.1006	U.S. Patent No. 8,921,316 (Dix)
Ex.1007	U.S. Publication No. 2016/0144025 A1 (Vitti)
Ex.1008	Center for Drug Evaluation and Research, “Clinical Pharmacology and Biopharmaceutics Review(s)” App. No. 125387Orig1s000 (2011) (“2011 Eylea® Clinical Review”)
Ex.1009	Product Information EYLEA® aflibercept (rch), (“AU Eylea® Label”)
Ex.1010	U.S. Publication No. 2015/0071920 A1 (Larson)
Ex.1011	U.S. Publication No. 2017/0232199 A1 (Fiedler)
Ex.1014	Robert L. Avery, MD et al., <i>INTRAVITREAL INJECTION TECHNIQUE AND MONITORING Updated Guidelines of an Expert Panel</i> , Retina, J. Retinal and Vitreous Diseases, 34, S1-S18 (2014)

¹ This list is not intended to be inclusive of all materials I considered in forming my opinions. See *supra* ¶ 3.

Ex.1015	Sahar Awwad et al., <i>Principles of Pharmacology in the Eye</i> , 174 Brit. J. Pharmacol. 4205 (2017)
Ex.1017	CATT Research Group, <i>Ranibizumab and bevacizumab for Neovascular Age-Related Macular Degeneration</i> , 364 NEJM 1897 (2011)
Ex.1019	Steven R. Cohen & Thomas W. Gardner, <i>Diabetic Retinopathy and Diabetic Macular Edema</i> , 55 Dev. Ophthalmol. 137 (2016)
Ex.1020	Arup Das, Paul G. McGuire & Sampathkumar Rangasamy, <i>Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets</i> , Ophthalmology (2015)
Ex.1022	Elia J. Duh, Jennifer K. Sun & Alan W. Stitt, <i>Diabetic retinopathy: current understanding, mechanisms, and treatment strategies</i> , JCI Insight (2017).
Ex.1024	K Ghasemi Falavarjani & QD Nguyen, <i>Adverse Events and Complications Associated with Intravitreal Injection of Anti-VEGF Agents: a Review of Literature</i> , Eye (2013)
Ex.1026	Allen C. Ho et al. <i>Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration</i> , 121 Ophthalmology 2181 (2014)
Ex.1029	Su-Eon Jin & Sung-Joo Hwang, <i>Ocular Delivery Systems for the Administration of Antibody Therapeutics</i> , J. Pharm. 47 Investig. 373 (2017)
Ex.1030	Lehman Brothers Presentation, 9 th Annual Global Healthcare Conference, Mar. 2006
Ex.1034	Quan Dong Nguyen, et al., <i>A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration</i> , 116 Ophthalmology 2141 (2009)

Ex.1035	Quan Dong Nguyen, et al., <i>Evaluation of Very High- and Very Low-Dose Intravitreal Aflibercept in Patients with Neovascular Age-Related Macular Degeneration</i> , 28 J. Ocular Pharmacology and Therapeutics 581 (2012)
Ex.1037	Lorena Perez-Gutierrez & Napoleone Ferrara, <i>Biology and therapeutic targeting of vascular endothelial growth factor A</i> , Nature Reviews Molecular Cell Biology (2023)
Ex.1039	Michael W. Stewart, <i>Clinical and Differential Utility of VEGF Inhibitors in Wet Age-Related Macular Degeneration: Focus on Aflibercept</i> , 6 Clin. Ophthalmol. 1175 (2012)
Ex.1041	George Trichonas & Peter K. Kaiser, <i>Aflibercept for the Treatment of Age-Related Macular Degeneration</i> , 2 Ophthalmol. Ther. 88 (2013)
Ex.1047	Wykoff et al., <i>Optimizing Anti-VEGF Treatment Outcomes for Patients with Neovascular Age-Related Macular Degeneration</i> , 24 J. Managed Care Specialty Pharm. S3 (2018)
Ex.1048	Macugen® 2011 Label
Ex.1050	Eylea® 2011 Label
Ex.1053	Eylea® 2016 Label
Ex.1054	Eylea® HD 2024 Label
Ex.1055	Lucentis® 2017 Label
Ex.1057	Vabysmo® 2022 Label
Ex.1058	Assessment Report, Eylea aflibercept, Committee for Medicinal Products for Human Use (CHMP), <i>European Medicines Agency Science Medicines Health</i> , Sept. 2012

Ex.1062	Napoleone Ferrara, <i>Vascular endothelial growth factor and age-related macular degeneration: from basic science to therapy</i> , Nature Medicine (2010).
Ex.1063	Roomasa Channa, Michael Smith & Peter A Campochiaro, <i>Treatment of macular edema due to retinal vein occlusions</i> , Clinical Ophthalmology (2011)
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Ex.2001	Excerpts from the File History of U.S. Appl. No. 17/384,070
Ex.2002	US 2018/0326126 (“Fiedler ’126”)
Ex.2003	Australian Dep’t of Health & Human Aging, Australian Public Assessment Report for Aflibercept (July 2012) (“AusPAR”)
Ex.2004	Ameya U. Borwankar et al., <i>Viscosity Reduction of a Concentrated Monoclonal Antibody with Arginine.HCl and Arginine.Glutamate</i> , 55 Ind. Eng. Chem. Rsch. 11225 (2016) (“Borwankar”)
Ex.2005	Neal Whitaker et al., <i>A Formulation Development Approach to Identify and Select Stable Ultra-High-Concentration Monoclonal Antibody Formulations with Reduced Viscosities</i> , 106 J. Pharmaceutical Scis. 3230 (2017) (“Whitaker”)
Ex.2008	AbbVie, Allergan, an AbbVie Company, and Molecular Partners Receive Complete Response Letter from FDA on Biologics License Application for Abicipar Pegol, AbbVie News Center (June 26, 2020), https://news.abbvie.com/2020-06-26-Allergan-an-AbbVie-Company-and-Molecular-Partners-Receive-Complete-Response-Letter-from-FDA-on-Biologics-License-Application-for-Abicipar-pegol (“AbbVie Press Release”)
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	<i>Age-Related Macular Degeneration</i> , 22 Expert Op. Emerging Drugs 235 (2017) (“Hussain”)
Ex.2011	Angus Liu, <i>Novartis Calls off 3 Beovu Trials Testing More Frequent Dosing on Concerns of Vision-Threatening Side Effect</i> , FiercePharma (June 1, 2021) (“Liu 2021”)
Ex.2012	Beovu Label (2024)
Ex.2013	Philip J. Rosenfeld & David J. Browning, <i>Editorial: Is This a 737 Max Moment for Brolucizumab?</i> , 216 Am. J. Ophthalmology A7 (2020) (“Rosenfeld”)
Ex.2014	J. Gaudreault et al., <i>Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) After a Single Intravitreal Administration</i> , 46 Invest. Ophthalmol Vis. Sci. 726 (2005) (“Gaudreault”)
Ex.2015	Public Trial Transcript Excerpts, <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , No. 22-cv-61 (N.D.W. Va.)
Ex.2018	Philip J. Rosenfeld et al., <i>Maximum Tolerated Dose of a Humanized Anti-Vascular Endothelial Growth Factor Antibody Fragment for Treating Neovascular Age-Related Macular Degeneration</i> , 112 Ophthalmology 1048 (2005) (“Rosenfeld 2005”)
Ex.2022	Rahul N. Khurana et al., <i>Two-Year Results of the Phase 3 Randomized Controlled Study of Abicipar in Neovascular Age-Related Macular Degeneration</i> , 128 Ophthalmology 1027 (2021) (“Khurana 2021”)
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Ex.2031	Molecular Partners, Molecular Partners to Regain Global Rights to Abicipar, Molecular Partners News Release Details (Aug. 8, 2021) https://investors.molecularpartners.com/news-releases/news-release-details/molecular-partners-regain-global-rights-abicipar (“Molecular Partners Press Release”)
Ex.2032	Novartis, <i>Novartis Reports One Year Results of Phase III MERLIN Study Evaluating Beovu® Every Four Week Dosing and Provides Update on Beovu Clinical Program</i> , Novartis Media Releases (May 28, 2021) https://www.novartis.com/news/media-releases/novartis-reports-one-year-results-phase-iii-merlin-study-evaluating-beovu-every-four-week-dosing-and-provides-update-beovu-clinical-program (“Novartis Press Release”)
Ex.2035	U.S. Food & Drug Admin., Eylea HD Approval Letter (Aug. 18, 2018) (“Eylea HD FDA Approval Letter”)
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Ex.2046	Deposition Transcript of Dr. Robert J. Falconer (May 27, 2026)
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Ex.2087	Judy E. Kim et al., <i>Short-Term Intraocular Pressure Changes Immediately After Intravitreal Injections of Anti-Vascular Endothelial Growth Factor Agents</i> , 146 Am. J. Ophthalmol. 930 (2008)
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Ex.2092	Jeffrey R. Sachs et al., <i>Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example</i> , 22 Clinical Cancer Rsch. 1318 (2016)
Ex.2094	Jiunn H. Lin, <i>Species Similarities and Differences in Pharmacokinetics</i> , 23 Drug Metabolism & Disposition 1008 (1995)
Ex.2095	Frank G. Holz et al., <i>Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular</i>

	<i>Degeneration: Chroma and Spectri Phase 3 Randomized Clinical Trials</i> , 136 JAMA Ophthalmol. 666 (2018)
Ex.2096	Neil M. Bressler et al., <i>Intraocular Pressure Outcomes After Lampalizumab Injections in Patients with Geographic Atrophy</i> , 142 JAMA Ophthalmol. 772 (2024)
Ex.2097	LabChem Inc., Material Safety Data Sheet: Congo Red (CAS No. 573-58-0)
Ex.2098	Agar Scientific Ltd., Safety Data Sheet: Congo Red (C.I. 22120)
Ex.2099	Santa Cruz Biotechnology, Safety Data Sheet: Amaranth (SC-214532)
Ex.2100	Eduardo B. Rodrigues et al., <i>Preclinical Investigation of the Retinal Biocompatibility of Six Novel Vital Dyes for Chromovitrectomy</i> , 29 Retina 497 (2009)
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Ex.2102	Ellen Kurek, <i>Conflicting Evidence over Stroke Risk from AMD Drug</i> , Pharmacy Times, available at https://www.pharmacytimes.com/view/conflicting-evidence-over-stroke-risk-from-amd-drug (last visited June 12, 2026)
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Ex.2104	Bevacizumab (Avastin®) Label 2017 (Avastin Label)

Ex.2105	James A. Hanley & Abby Lippman-Hand, <i>If Nothing Goes Wrong, Is Everything All Right? Interpreting Zero Numerators</i> , 249 JAMA 1743 (1983)
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Ex.2107	Deepika Malik et al., <i>Safety Profiles of Anti-VEGF Drugs: Bevacizumab, Ranibizumab, Aflibercept and Ziv-Aflibercept on Human Retinal Pigment Epithelium Cells in Culture</i> , 98 Brit. J. Ophthalmol. i11 (2014)
Ex.2108	Robert L. Avery et al., <i>Systemic Pharmacokinetics and Pharmacodynamics of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab</i> , 37 Retina 1847 (2017)
Ex.2109	U.S. Food & Drug Admin., <i>Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers</i> (July 2005)
Ex.2110	Brandon G. Busbee et al., <i>Twelve-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration</i> , 120 Ophthalmology 1046 (2013)
Ex.2111	U.S. Food & Drug Admin., <i>Postmarketing Adverse Event Reporting Compliance Program</i> , https://www.fda.gov/drugs/surveillance-post-drug-approval-activities/postmarketing-adverse-event-reporting-compliance-program (last visited June 16, 2026)
Ex.2112	U.S. Food & Drug Admin., <i>Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients</i> (May 2005)
Ex.2113	Sophie Postel-Vinay et al., <i>Towards New Methods for the Determination of Dose Limiting Toxicities and the Assessment</i>

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Ex.2115	V. Burckbuchler et al., <i>Rheological and Syringeability Properties of Highly Concentrated Human Polyclonal Immunoglobulin Solutions</i> , 76 Eur. J. Pharmaceutics & Biopharmaceutics 351 (2010)
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Ex.2124	Daniel Y. Choi, <i>Sustained Elevated Intraocular Pressures After Intravitreal Injections of Bevacizumab, Ranibizumab, and Pegaptinib</i> , 31(6) Retina 1028 (2011)

Ex.2126	Roche, <i>Angiogenesis Highlights</i> (Feb. 16, 2021)
Ex.2131	Eylea HD® Highlights of Prescribing Information (Apr. 2026)
Ex.2140	U. Schmidt-Erfurth et al., <i>Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration</i> , 121 <i>Ophthalmology</i> 193 (2014)
Ex.2141	Regeneron, Regeneron Announces Encouraging Topline Phase 2 Data of High-dose aflibercept in Wet Age-related Macular Degeneration, Regeneron Press Release Details, (Aug. 24, 2021), https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-topline-phase-2-data-high-dose
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