

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI SWISSBIOSIM GMBH
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Case No. 2025-01269
U.S. Patent No. 10,828,345 B2

**EXPERT DECLARATION OF DR. JOHN C. GALANIS
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 10,828,345**

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1004	Curriculum Vitae of Dr. John C. Galanis
1005	Jocelyn Holash et al., <i>VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects</i> , 99 PROC. NAT’L ACAD. SCI. 11393 (2002) (“Holash”)
1006	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) (“Nguyen-2009”)
1007	James A Dixon et al., <i>VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration</i> , 18 EXPERT OPINION ON INVESTIGATIONAL DRUGS 1573 (2009) (“Dixon”)
1008	Adis R&D Profile, <i>Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye</i> , 9 DRUGS R&D 261 (2008) (“Adis”)
1009	U.S. Patent No. 9,254,338 B2 (“the ’338 patent”)
1010	U.S. Patent No. 7,531,173 B2 (“the ’173 patent”)
1012	U.S. Patent No. 7,374,758 B2 (“the ’758 patent”)
1013	U.S. Patent No. 10,888,601 B2 (“the ’601 patent”)
1014	IPR2022-01226, <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , Final Written Decision for U.S. Patent No. 10,888,601 (Jan. 9, 2024) (“FWD IPR2022-01226”)
1015	IPR2021-00881, <i>Mylan Pharmaceuticals Inc., et al. v. Regeneron Pharmaceuticals, Inc.</i> , Final Written Decision for U.S. Patent No. 9,254,338 (Nov. 9, 2022) (“FWD IPR2021-00881”)
1016	Jeffery S. Heier, <i>VEGF Trap-Eye for Exudative AMD</i> , RETINAL PHYSICIAN, Apr. 2009 (“Heier-2009”)
1017	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1), NCT00509795, ClinicalTrials.gov (Apr. 28, 2009), https://clinicaltrials.gov/ct2/show/NCT00509795 (“NCT-795”)
1018	VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2), NCT00637377, ClinicalTrials.gov (Mar. 17, 2008),

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1019	Regeneron. [Press Release] <i>Positive Interim Phase 2 Data Reported for VEGF Trap-Eye in Age-Related Macular Degeneration</i> (Mar. 27, 2007), https://newsroom.regeneron.com/news-releases/news-releasedetails/positive-interim-phase-2-data-reported-vegf-trap-eye-agerelated?releaseid=394105 (“Regeneron (27-March-2007)”)
1020	Regeneron. [Press Release] <i>Regeneron and Bayer HealthCare Initiate Phase 3 Global Development Program for VEGF Trap-Eye in Wet Age-Related Macular Degeneration (AMD)</i> (Aug. 2, 2007), https://investor.regeneron.com/news-releases/news-releasedetails/regeneron-and-bayer-healthcare-initiate-phase-3-global (“Regeneron (2-August-2007)”)
1021	Regeneron. [Press Release] <i>Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration</i> (Apr. 28, 2008), http://investor.regeneron.com/releasedetail.cfm?releaseid=394066 (“Regeneron (28-April-2008)”)
1022	Regeneron. [Press Release] <i>Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age Related Macular Degeneration</i> (May 8, 2008), http://investor.regeneron.com/releasedetail.cfm?ReleaseID=394065 (“Regeneron (2008-May-08)”)
1023	Regeneron. [Press Release] <i>Regeneron and Bayer HealthCare Announce VEGF Trap-Eye Achieved Durable Improvement in Vision Over 52 Weeks in a Phase 2 Study in Patients with Age Related Macular Degeneration</i> (Aug. 19, 2008), https://investor.regeneron.com/news-releases/news-releasedetails/regeneron-and-bayer-healthcare-announce-vegf-trap-eyeachieved?ReleaseID=394056 (“Regeneron (19-August-2008)”)
1024	Patrick S. Sharp, <i>The Role of Growth Factors in the Development of Diabetic Retinopathy</i> , 44 METABOLISM No. 10, Suppl. 4, 72-75 (Oct. 1995) (“Sharp”)
1025	David M. Brown & Carl D. Regillo, <i>Anti-VEGF Agents in the Treatment of Neovascular Age-Related Macular Degeneration: Applying Clinical Trial Results to the Treatment of Everyday Patients</i> , 144 AM. J. OPHTHALMOLOGY 627 (2007) (“Brown”)

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1026	Talia N. Crawford, et al., <i>Diabetic Retinopathy and Angiogenesis</i> , 5 Current Diabetes Reviews, 8-13 (2009) (“Crawford”)
1027	Napoleone Ferrara & Robert S. Kerbel, <i>Angiogenesis as a Therapeutic Target</i> , 438 NATURE 967 (2005) (“Ferrara-2005”)
1028	Ziad F. Bashshur et al., <i>Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration</i> , 142 AM. J. OPHTHALMOLOGY 1 (2006) (“Bashshur”)
1029	LUCENTIS® Prescribing Information (2006) (“Lucentis”)
1031	Jeffrey S. Heier et al., <i>Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration</i> , 119 OPHTHALMOLOGY 2537 (2012) (“Heier-2012”)
1032	J.S. Rudge et al., <i>VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene®-Based Discovery of the Next Generation of Angiogenesis Targets</i> , 70 COLD SPRING HARBOR SYMPOSIA QUANTITATIVE BIOLOGY 411 (2005) (“Rudge”)
1033	Quan Dong Nguyen et al., <i>A Phase I Trial of an IV-Administered Vascular Endothelial Growth Factor Trap for Treatment in Patients with Choroidal Neovascularization due to Age-Related Macular Degeneration</i> , 113 OPHTHALMOLOGY 1522 (2006) (“Nguyen-2006”)
1034	John S. Rudge et al., <i>VEGF Trap Complex Formation Measures Production Rates of VEGF, Providing a Biomarker for Predicting Efficacious Angiogenic Blockade</i> , 104 PNAS 18363 (2007) (“Rudge-2007”)
1035	John S. Rudge et al., <i>Clinical Development of VEGF Trap</i> , ANGIOGENESIS, Chpt. 36 (William D. Figg & Judah Folkman eds. 2008) (“Rudge-2008”)
1036	Candelaria Gomez-Manzano et al., <i>VEGF Trap Induces Antiglioma Effect at Different Stages of Disease</i> , 10 NEURO-ONCOLOGY 940 (2008) (“Gomez-Manzano”)
1037	Regeneron Pharm., Inc., Quarterly Report (Form 10-Q) (Sept. 30, 2009) (“2009 10-Q”)
1038	P Mitchell et al., <i>Ranibizumab (Lucentis) in Neovascular Age-Related Macular Degeneration: Evidence from Clinical Trials</i> , 94 BRIT. J. OPHTHALMOLOGY 2 (2009) (date of online publication) (“Mitchell”)

Exhibit	Description
1039	Regeneron. [Press Release] <i>VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting</i> (Sept. 28, 2008), https://investor.regeneron.com/newsreleases/news-release-details/vegf-trap-eye-final-phase-2-resultsage-related-macular?ReleaseID=393906 (“Regeneron (28-September-2008)”)
1040	Regeneron. [Press Release] <i>Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)</i> (Sept. 14, 2009), https://investor.regeneron.com/news-releases/newsrelease-details/enrollment-completed-regeneron-and-bayerhealthcare-phase-3?ReleaseID=408872 (“Regeneron (14-September-2009)”)
1041	Napoleone Ferrara et al., <i>Development of Ranibizumab, and Anti-Vascular Endothelial Growth Factor Antigen Binding Fragment, as Therapy for Neovascular Age-Related Macular Degeneration</i> , 26 RETINA, THE J. OF RETINAL AND VITREOUS DISEASES, No. 8, 859-870 (2006) (“Ferrara-2006”)
1042	Heinrich Heimann, <i>Intravitreal Injections: Techniques and Sequelae</i> , MEDICAL RETINA 67 (Frank G. Holtz & Richard F. Spaide eds. 2007) (“Heimann-2007”)
1043	U.S. Application Publication No. 2007/0190058 (“the ’058 application”)
1044	Pascale Massin, et al., <i>Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study)</i> , 33 DIABETES CARE, No. 11 (Nov. 2010) (“Massin”)
1045	Anne F. Fung, et al., <i>An Optical Coherence Tomography-Guided, Variable Dosing Regimen with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration</i> , AM. J. OPHTHAMOLOGY 143:566-583 (Apr. 2007) (“Fung”)
1052	Regeneron. [Press Release] <i>VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients with Diabetic Macular Edema</i> (Feb. 18, 2010), https://investor.regeneron.com/news-releases/news-release-details/vegf-trap-eye-shows-positive-results-phase-2-study-patients (“Regeneron (18-Feb-2010)”)

I. INTRODUCTION

1. I, John C. Galanis, submit this Expert Declaration on behalf of Petitioner Fresenius Kabi SwissBioSim GmbH (“Fresenius” or “Petitioner”) in the above captioned *Inter Partes* Review (“IPR”).

2. I have been retained by Petitioner to provide my technical expertise and expert opinions regarding U.S. Patent No. 10,828,345 (Ex. 1001, “the ’345 patent”), which I understand is assigned to Regeneron Pharmaceuticals, Inc. (“Regeneron”). I further understand that Petitioner is petitioning for IPR of the ’345 patent, and is requesting that the United States Patent and Trademark Office (“USPTO”) cancel claims 1-11 of the ’345 patent as unpatentable. My opinions in this expert declaration support Petitioner’s request for IPR of the ’345 patent and the cancellation of claims 1-11 (the “Challenged Claims”).

II. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

3. My educational background, career history, publications, and other relevant qualifications are summarized here. My complete curriculum vitae can be found at Ex. 1004.

4. I am a board certified and licensed ophthalmologist with more than 35 years of experience in the medical and surgical management of various eye diseases.

5. I earned my medical degree from St. Louis University School of Medicine in 1984. Thereafter, I received residency training in ophthalmology also at St. Louis University School of Medicine where I served as chief resident in 1988.

6. I also completed fellowship training in glaucoma at the University of Southern California Estelle Doheny Eye Institute in 1988.

7. I am currently the medical director of the Galanis Cataract and Laser Eye Center in St. Louis, Missouri. I am also on staff at St. Luke's Hospital in St. Louis, Missouri.

8. Currently, I am also an Assistant Clinical Professor of Ophthalmology at St. Louis University School of Medicine and Assistant Adjunct Professor at the University of Missouri – St. Louis College of Optometry.

9. I am a member of the American Academy of Ophthalmology, the American Society of Cataract and Refractive Surgery, the St. Louis Ophthalmological Society and am a Fellow of the American College of Surgeons. I also sit on the Board of Directors for the St. Louis Society for the Blind.

10. I have received several awards throughout my career and have been recognized as one of the “top doctors” by St. Louis Magazine.

III. MATERIALS CONSIDERED

11. In coming to my opinions set forth herein, I have reviewed and/or considered each of the Challenged Claims and relevant portions of their prosecution histories, as well as background literature and prior art as cited throughout this Declaration. The bases for my opinions include the prior art and observations cited

in this Declaration, my education, and more than 30 years experience as practicing, board certified ophthalmologist.

IV. SCOPE OF WORK

12. As noted above, I have been retained by Petitioner as an expert in this matter to provide my various opinions regarding the '345 patent including the Challenged Claims. I receive compensation for my services. No part of my compensation is dependent upon my opinions in this case or the outcome of this case. I do not have any current or past affiliation with Regeneron or the named inventor on the '345 patent.

V. SUMMARY OF OPINIONS

13. I have been asked to provide my opinion regarding whether the Challenged Claims of the '345 patent are invalid/unpatentable.

14. It is my opinion that the claims 1-9 of the '345 patent are invalid/unpatentable as anticipated by each of Dixon, NCT-795, NCT-377, and Regeneron (8-May-2008); and/or obvious over Dixon alone or in view of NCT-377.

15. It is also my opinion that claims 10 and 11 of the '345 patent are invalid/unpatentable as obvious over any one of Dixon, NCT-377, NCT-795, Regeneron (8-May-2008) in view of Regeneron (18-Feb-2010) and the knowledge of a person of ordinary skill in the art as of the alleged priority date (November 2011).

VI. LEGAL STANDARD

16. I am not a patent lawyer and therefore Counsel has informed that the following patent law is applicable to the relevant issues in this case. In coming to my opinions in this Declaration, I have applied my understanding of the below patent law principles.

A. The Presumption of Validity

17. I understand that an issued U.S. patent is presumed valid. I also understand that each Challenged Claim is presumed valid. To find a patent claim invalid/unpatentable, a defendant bears the burden of proving invalidity by preponderance of the evidence. I am informed that this preponderance of the evidence standard means that Petitioner must show that invalidity/unpatentability is more probable than not.

B. Claim Construction and Level of Ordinary Skill in the Art

18. I understand that there is a two-step process that must be applied in order to determine whether a Challenged Claim is anticipated or obvious based on the prior art: First, the patent claims must be construed. Second, the properly construed claims must be examined in view of the scope and content of the prior art.

19. Regarding construing the claim terms, I have been told the claim term(s) should be analyzed under their ordinary and customary meaning as

understood from the perspective of one of ordinary skill in the art at the time of the invention, taking into account the claim language itself, patent specification, and prosecution history pertaining to the patent, as well as relevant extrinsic evidence.

20. I have also been informed that the validity of a patent claim is evaluated from the perspective of a “person of ordinary skill in the art” (“POSA”) or a “skilled artisan” at the time of the invention. I understand that a POSA is a hypothetical person considered to have the skill level and knowledge of a particular field related to an alleged invention claimed in a patent.

21. I also understand that a POSA is presumed to have before them all of the relevant prior art that was publicly available at the time of the invention. A POSA can be more than one person and/or have access to a team of people at the time of the invention.

C. Anticipation

22. I understand that a patent claim may be invalid if it is anticipated by the prior art. To be anticipated, a single prior art patent or printed publication read from the perspective of a POSA at the time of the patent filing—must either expressly or inherently disclose each element or step of the patented method.

23. I have also been informed that for purposes of determining anticipation by a prior art reference, when a reference or information is incorporated in the anticipatory prior-art reference, the incorporated reference/information is effectively

part of the anticipatory prior art reference. To incorporate material by reference, I understand that the anticipatory reference must identify with particularity what specific material it incorporates and clearly indicate where that material is found in the incorporated reference.

D. Obviousness.

24. I understand that a patent claim may be invalid if, as a whole, it would have been obvious to a POSA as of the effective filing date of the patent claim. A patent claim is obvious if a single prior-art reference/disclosure or a combination of prior-art references/disclosures and a POSA's knowledge would have rendered the claimed invention an obvious implementation as of the effective filing date of the patent. Obviousness can be shown by demonstrating that a POSA would have been motivated to combine references and/or knowledge with a reasonable expectation of success in applying the prior art teachings.

25. I also understand that absent demonstration of criticality, ranges of a parameter recited in Challenged Claims, such as a range of administration rates or frequency of administration, or other such features, do not indicate nonobviousness over prior art that disclosed a different value for the same parameter.

26. Whether a patent claim would have been obvious requires an analysis of the scope and content of the prior art and a comparison of the prior art to the patent claim in light of the level of ordinary skill in the pertinent art.

27. I also understand that when the prior art provides the means of making the invention with a reasonable expectation of success and the patentee merely verifies the expectation through routine testing, the claims are obvious.

28. I understand that the named inventor's path to making or conceiving of the claimed subject matter cannot, however, serve to demonstrate the subject matter's obviousness. Therefore, in my analysis set forth herein, I did not use the inventor's path, nor did I start with patent claims and work backwards. In my analysis, I reviewed the prior art leading up to the effective filing date of the patent and determined what conclusions a POSA would have reached about obvious implementations, and then applied my opinions to the Challenged Claims.

29. I understand that one must also consider if there is evidence of objective indicia (or "secondary consideration") of non-obviousness, which may include commercial success of the claimed subject matter, fulfilling a long-felt but unresolved need, copying of the claimed subject matter, failure of others to make the claimed subject matter, praise for the invention, and/or unexpected results. If any of these secondary considerations is asserted, then I understand that a patent owner must also show a nexus or connection between the secondary consideration and the inventive aspect of the claims to which that secondary consideration allegedly apply.

VII. PERSON OF ORDINARY SKILL IN THE ART.

30. As noted above, I have been informed by counsel that my analysis is to be conducted from the perspective of a POSA and what a POSA would have known, understood, and be familiar with in view of the relevant prior art, and that such person is not an automaton, but rather a person of ordinary creativity.

31. I have also been informed by counsel that in defining a POSA, the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field.

32. After considering the above-mentioned factors, it is my opinion that a POSA would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in: (1) developing treatments for angiogenic eye disorders, such as AMD and diabetic retinopathy, including through the use of VEGF antagonists, or (ii) treating of angiogenic eye disorders through the use of VEGF antagonists.

33. I note that the PTAB has previously agreed with my proposed definition for a POSA. In the context of U.S. Patent No. 9,254,338 (“the ’338 patent”), which shares the same specification and is therefore related to the ’345 patent (*Compare* Ex. 1001 *with* Ex. 1009), the PTAB found that “Petitioner’s definition of one of ordinary skill in the art[,] [which is substantively the same as the one I propose,] is reasonable and consistent with the ’338 patent and the prior art of record.” Ex. 1015 at 10. Similarly, the PTAB, in the context of U.S. Patent No. 10,888,601 (“the ’601 patent”), which also shares the same specification and recites substantively similar claims as the Challenged Claims (*compare* Ex. 1001 *with* Ex. 1013), determined that “we find Petitioner’s definition to be consistent with the level of skill in the art.” Ex. 1014 at 70.

VIII. BACKGROUND

34. Below I provide a discussion of the relevant knowledge, medical background, and treatment approaches that a POSA would have known as of the priority date of the ’345 Patent. The medical background I discuss in this Section would have been common knowledge to a POSA as of the priority dates.

35. Appreciating the knowledge and experience of a POSA in the treatment of angiogenic eye disorders in a patient is pertinent to my claim-specific analysis of each of the Challenged Claims, which analysis appears in Section XI of this Declaration. My analysis shows that the Challenged Claims merely reflect the

routine methods known and utilized by physicians and a POSA, as of the priority date of the '345 patent, in the treatment of angiogenic eye disorders.

A. Angiogenic Eye Disorders/Ocular Angiogenesis

36. Angiogenic eye disorders is related to a broad spectrum of conditions that lead to vision loss as a result of angiogenesis. Angiogenesis is the process of new capillaries forming out of preexisting blood vessels. Typically, angiogenesis helps the body heal from wounds and serves other vital functions, including supplying oxygen-rich blood to organs and tissue. In the case of angiogenic eye disorders, however, angiogenesis becomes abnormal or excessive leading to vascular permeability which in turn leads to retinal edema¹, vascular fragility² resulting in hemorrhage or fibrovascular proliferation³ with tractional⁴ and rhegmatogenous⁵ retinal detachment. Below I further discuss angiogenic eye disorders and some of the ocular angiogenesis sub-types.

1. VEGF And Angiogenic Disorders

¹ Swelling in the macula, the central part of the retina responsible for sharp, central vision.

² Condition where the blood vessels become weak and prone to breakage, resulting in easy bruising and bleeding.

³ Condition characterized by the abnormal growth of new blood vessels (neovascularization) and fibrous tissue on the surface of the retina.

⁴ Retinal detachment caused by scar tissue or membranes pulling the retina away from the back of the eye.

⁵ A tear or break in the retina that allows fluid to seep behind it and separate the retina from the underlying tissue.

37. A critical component of ocular angiogenesis is the Vascular Endothelial Growth Factor or “VEGF,” which is a signaling protein that stimulates the formation of blood vessels. Ex. 1021 at 2. VEGF creates new blood vessels during embryonic development and after injury, and creates new pathways for blocked vessels. However, overexpression of VEGF is implicated in tumor growth. Ex. 1027 at 2. Thus, VEGF inhibitors or antagonists were identified as potential therapies leading to extensive research and development including clinical testing. *Id.* at 5.

38. VEGF has also been implicated in ocular angiogenesis. By 2005, POSAs recognized that

VEGF may play a key pathological role in vascular eye diseases, in particular in diabetic edema and retinopathy settings, and in age related macular degeneration. In these diseases, excess VEGF is thought to result in vascular leak that contributes to abnormal swelling of the retina and resulting vision impairment, as well as in the abnormal growth of choroidal and retinal vessels that can destroy normal retinal architecture.

Ex. 1032 at 4. *See also*, Ex. 1027 at 5-6 (disclosing that VEGF may lead to fragility of new blood vessels in the eye, a condition associated with wet AMD).

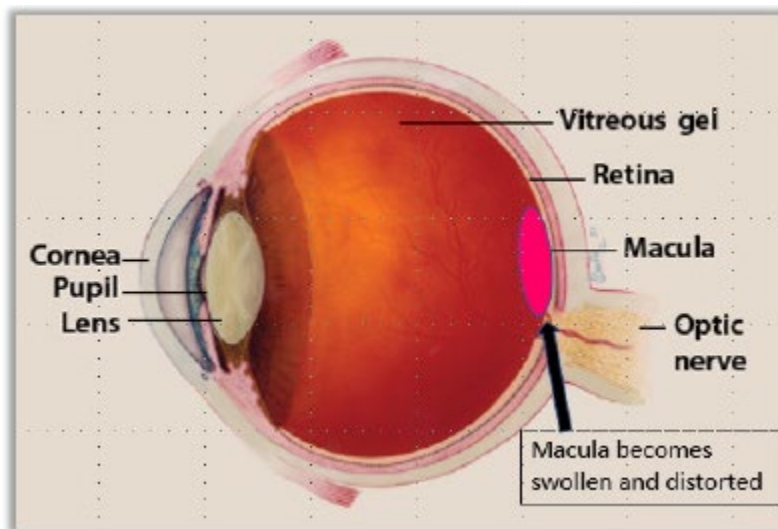
39. Below I discuss some of the major angiogenic eye disorders that are implicated by VEGF.

a) Age-Related Macular Degeneration (AMD)

40. AMD is a common eye condition and a leading cause of vision loss among people age 60 or older. It causes damage to the macula, a small spot near the

center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead.

41. When angiogenesis takes place beneath the retina resulting in blood and/or fluid leaking that causes disruption and dysfunction of the retina, AMD is classified as “wet” and can be visualized as follows:



Over time this will cause scarring or formation of a disciform and associated vision loss.

42. Early treatment for wet AMD has traditionally focused on laser and photodynamic therapy, in which portions of the eye are cauterized to prevent further angiogenesis. However, as of the priority date of the '345 patent, POSAs had come to realize that this treatment approach had limited efficacy and was accompanied by serious risks including vision loss. Ex. 1007 at 1 (“[Patients treated with

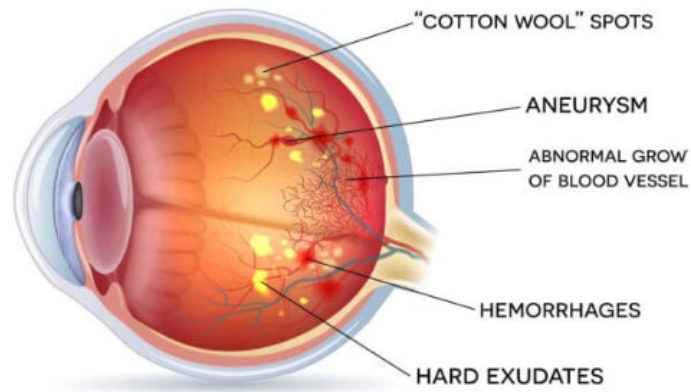
photodynamic therapy] continued to experience a decline in visual acuity and the treatment was of questionable cost and effectiveness.”).

2. Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME)

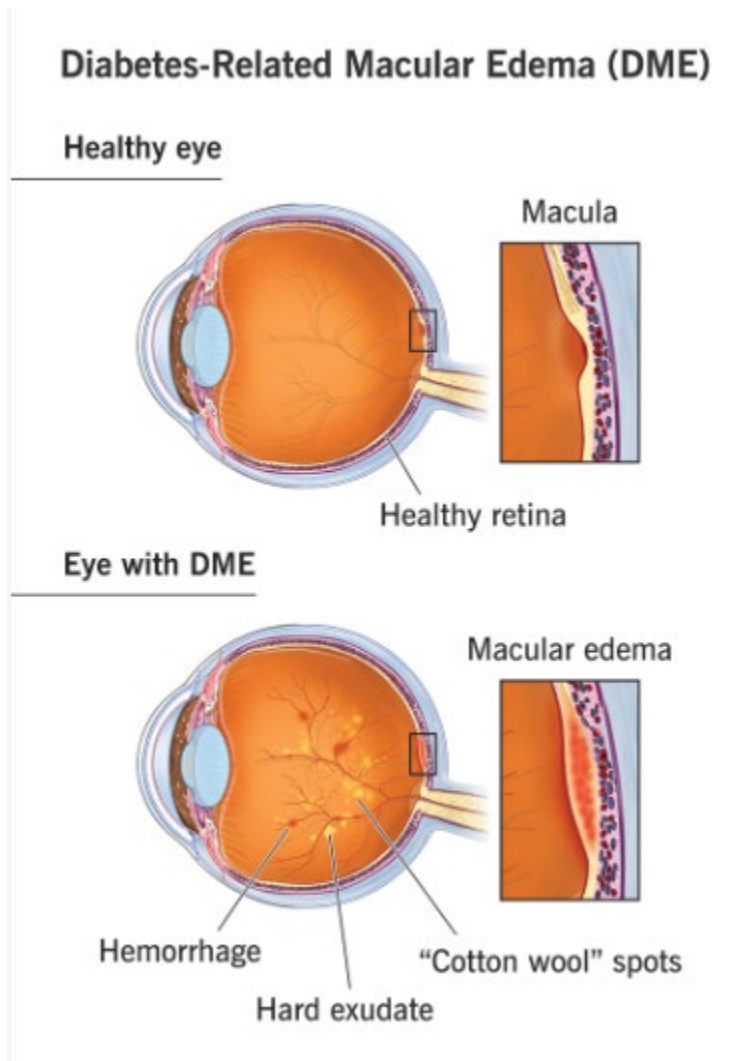
43. **Diabetic retinopathy** is a complication of diabetes that results from chronically high blood sugar levels damaging the blood vessel in the retina. The retina is the part of the eye that converts light into neural signals that the brain can interpret as vision. Diabetic retinopathy can cause blood vessels in the retina to swell or leak, leading to distorted or blurred vision. In severe cases, it can cause the blood vessels to be damaged, resulting in growth of new, abnormal blood vessels on the retina and bleeding, which can lead to blindness.

44. DR and AMD are similar in that both diseases affect the eye near the retina and result from expression of VEGF leading to angiogenesis. However, the location of AMD and diabetic retinopathy differ slightly. Diabetic retinopathy occurs within the retina and its blood vessels, whereas AMD involves blood vessels or drusen that grow under the retina. Diabetic Retinopathy can be visualized as follows:

DIABETIC RETINOPATHY



45. **Diabetic macular edema** is a complication of DR wherein there is “build-up of fluid (edema) in ... the macula.” It can be visualized as follows:



DME is the most common cause of vision loss among people with DR.

46. As of 2011 it was known that “[d]iabetic retinopathy [is] a secondary microvascular complication of diabetes mellitus” and “is the leading cause of blindness in the United States amongst individuals age 20 to 64.” Ex. 1026 at 1. “Two major retinal problems cause most of the diabetes-related vision loss: diabetic macular edema and complications from abnormal retinal blood vessels growth, angiogenesis.” *Id.*

47. It was also known that “[h]igh glucose,” which is a major component of diabetes, “induces hypoxia in retinal tissue, thus leading to the production of VEGF-A.” *Id.* This production of VEGF-A leads to angiogenesis. *Id.* (“VEGF-A is a powerful angiogenic inducer.”). However, due to diabetes, the “new vessels formation becomes problematic because they are fragile and highly permeable” and when these “delicate vessels are disrupted easily by vitreous traction [it] leads to hemorrhage into the vitreous cavity or the preretinal space. This stage of proliferative diabetic retinopathy (PDR) is most concerning since it poses the greatest threat of vision loss.” *Id.* at 2; *see also*, Ex. 1024 at 1 (“Proliferation of retinal blood vessels is one of the most striking features of advanced diabetic retinopathy. This feature has led to the conclusion that the normal balance of growth factors, which usually serves to keep angiogenesis in check, is disturbed in diabetic retinopathy.”); *id.* (“Proliferative diabetic retinopathy is one of the few examples of human pathological conditions in which abnormal growth of new vessels is one of the primary features.”).

48. Thus by 2011, it was well recognized that “[s]ince VEGF-A is a powerful angiogenic inducer, utilizing anti-VEGF treatments has proved to be a successful protocol in the treatment of proliferative diabetic retinopathy.” *Id.* In fact, ranibizumab was being used by POSAs as a treatment for diabetic retinopathy.

Ex. 1024 at 5 (“Ranibizumab is administered intravitreally through injection into the pars plana.”).

B. VEGF Antagonist

49. As I discuss above, long before the priority date of the '345 patent, it was well known that VEGF plays a crucial role in angiogenesis that can lead to eye disorders such as AMD and DME. Thus, it is no surprise that as of 2011, it was recognized that VEGF inhibitors would be a useful tool in the treatment of angiogenesis eye disorders. *See, e.g.*, Ex. 1021 at 2 (“[b]lockade of VEGF, which can prevent abnormal blood vessel formation and vascular leak, has proven beneficial in the treatment of wet AMD and VEGF inhibitor”).

50. Bevacizumab was the first of these VEGF inhibitors. Ex. 1027 at 1, 971. It was initially approved to treat only cancer, but as of 2011 it was routinely used off-label for the treatment of AMD (via intravitreal injection) with some promising results. *See, e.g.*, Ex. 1028 at 1. Another VEGF inhibitor, ranibuzimab, had also “been approved for treatment of patients with this condition.” Ex. 1021 at 2. Ranibuzimab is a humanized monoclonal Fab fragment capable of blocking the activity of VEGF-A and marketed under the name LUCENTIS®. Ex. 1029. It was approved in 2006 and was originally indicated for monthly 0.5 mg intravitreal administration for the treatment of wet AMD.

C. VEGF Trap-Eye/Aflibercept

51. As of 2011 another VEGF inhibitor, VEGF Trap-Eye or “aflibercept” was undergoing clinical studies to seek FDA regulatory approval for the treatment of angiogenesis eye disorders. VEGF Trap-Eye or aflibercept is a VEGF blocker developed by Regeneron. “Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGF-1 and -2 combined with a human IgG Fc fragment (figure 1)[:]

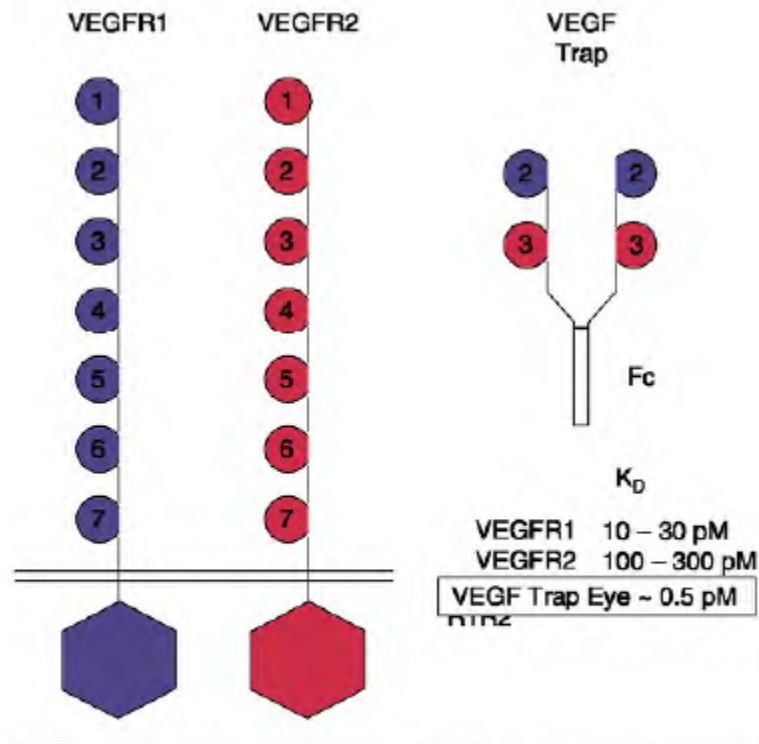


Figure 1. Schematic diagram of VEGF Trap-Eye, a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.

Ex. 1007 at 3, 4 (Fig. 1); *see also*, Ex. 1021 at 2 (“VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PlGF).”).

52. As early as 2002, in Holash (Ex. 1005), Regeneron had publicized its development work leading to VEGF Trap-Eye in. Regeneron disclosed that

The parental VEGF-Trap was created by fusing the first three Ig domains of VEGFR1 to the constant region (Fc) of human IgG1. VEGF-Trap Δ B1 was created by removing a highly basic 10-aa stretch from the third Ig domain of the parental VEGF-Trap. VEGF-Trap Δ B2 was created by removing the entire first Ig domain from VEGF-Trap Δ B1. VEGF-TrapR1R2 was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.

Ex. 1005 at 1-2. However, Regeneron recognized that “Despite its high affinity, the VEGFR1-Fc is not a feasible clinical candidate because of its poor pharmacokinetic profile[.]” *Id.* at 2. Regeneron went on to disclose how it “[r]eengineer[ed] [p]arenteral VEGF-Trap to [I]mprove [I]ts [P]harmacokinetic [p]rofile[:]

We postulated that these poor pharmacokinetic properties might be due to the high positive charge of [VEGF-Trap] (pI 9.4)... On review of the charge density in the parental molecule, we noted a high basic stretch of 10 amino acids in the third Ig domain of VEGFR1 To reduce the charge, this region was excised, ... It was also noted that the first Ig domain of VEGFR1 had a basic pI, and we thus decided to test removal of this domain as well as the above-noted basic region Finally, because the third Ig domain of VEGFR2 has a lower pI than the corresponding domain of VEGF1, we simply switched these domains to

make a Trap in which the second Ig domain of VEGF1 is directly fused to the third Ig domain of VEGF2; this trap was termed VEGF-Trap_{R1R2} VEGF-Trap_{R1R2} had an AUC that was almost 1,000 fold higher than that of the parenteral VEGF-Trap.

Id.

53. By 2011, VEGF-Trap_{R1R2} was identified as VEGF Trap-Eye. *See, e.g.,* Ex. 1010 at 1:48-52 (“[i]n a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap_{R1R2}) comprising the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2.”). Also by 2011, the further purified version of VEGF Trap-Eye “formulated with different buffers and different concentrations (for buffers in common) suitable for the comfortable, non-irritating direct injection into the eye” was known as “aflibercept.” Ex. 1007 at 1 (“One promising new drug is aflibercept (VEGF Trap-Eye)”; *id.* at 3 (“VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure.”) *See, also,* Ex. 1034 at 1, 8. (discussing VEGF Trap; including “aflibercept” as a keyword; and citing back to Holash (endnote 20)); Ex. 1016 at 1, 3 (disclosing description of the pharmacokinetics of VEGF Trap-Eye and for that discussion citing back to the data presented in Holash for VEGF Trap_{R1R2}); Ex. 1036 at 1, 6 (disclosing “a new anti-VEGF agent, VEGF Trap/aflibercept (henceforth referred to as VEGF Trap), has been developed by incorporating

domains of both VEGF receptor 1 (VEGFR1) and VEGFR-2 fused to the constant region of human immunoglobulin G1”, and citing Holash).

54. As such, Regeneron explained long before the priority date of the ’345 patent that VEGF Trap-Eye/aflibercept “has prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*,” and that it is intended to treat disorders associated with increased angiogenesis. (Ex. 1005 at 1); and that it “performs much better *in vivo*” than parenteral VEGF Trap “presumably because of its dramatically enhanced pharmacokinetic profile.” *Id.* at 3-4.

55. Regeneron also disclosed that the efficacy of VEGF Trap-Eye/aflibercept was equal to or better than anti-VEGF antibodies, which led the authors to conclude that the efficacious dose of VEGF Trap-Eye may be lower than that of monoclonal anti-VEGF antibody. *Id.* at 5. They also concluded that VEGF Trap-Eye may be useful in the treatment of retinopathies in view of the role that angiogenesis plays in such disorders. *Id.*

56. Others in the field similarly understood that “[t]he binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of bevacizumab or

ranibizumab”⁶ and the “greater affinity could translate into...a substantially longer duration of action in the eye, allowing for less frequent dosing, as supported by early clinical trials.” Ex. 1031 at 3.

57. Prior art publications disclosing Regeneron’s subsequent investigations disclosed that VEGF Trap-Eye could be useful in treating angiogenic eye disorders because it blocks VEGF-A, which has been shown to exhibit positive results in the treatment of wet AMD. Ex. 1032 at 1. Those investigations also showed that VEGF Trap-Eye may be useful in treating diabetic edema, DR, and AMD. *Id.* at 4 (disclosing that “VEGF Trap has demonstrated impressive efficacy in an assortment of animal models of [diabetic edema and retinopathy, and in AMD]”); *id.* (“These preclinical results support a role for VEGF blockade, and in particular for local delivery of the VEGF Trap, in multiple vascular eye diseases ranging from AMD and diabetic eye diseases to corneal injury and transplantation.”); *id.* at 4-5 (“Initial clinical studies in human patients suffering from both AMD and diabetic edema and retinopathy appear quite promising, with evidence in early trails that the VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity.”). Preclinical studies with VEGF Trap showed that it was able to inhibit choroidal and corneal neovascularization,

⁶ Though bevacizumab and ranibizumab are both anti-angiogenic VEGF inhibitors that bind to VEGF, they have different molecular structures. *See, e.g.*, Ex. 1041 at 4-8.

suppress vascular leak in the retina, and promote the survival of corneal transplants by inhibiting neovascularization. Ex. 1032 at 1.

58. By 2006, preliminary clinical trials had shown that “VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity.” *Id.* at 4-5; *see also*, Ex. 1033 at 9. As a result, VEGF-Trap thereafter was the subject of additional clinical studies related to vascular eye diseases. Ex. 1032 at 5; *see also*, Ex. 1035 at 5-6.

59. In view of these disclosures, a POSA as of 2011 would have understood the VEGF Trap_{R1R2} nomenclature to reference a single molecule, which a POSA would have understood was the single agent that Regeneron had in clinical trials and which Regeneron was calling both aflibercept and VEGF Trap-Eye. Indeed, the only difference between VEGF Trap and aflibercept as disclosed in Dixon was with respect to the purification and formulation steps. Ex. 1037 at 19 (“VEF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications.”).

D. Regeneron’s VEGF Trap-Eye Aflibercept Clinical Studies

60. As discussed above, Regeneron conducted research into VEGF Trap-Eye/aflibercept beginning in the early 2000’s and began publicizing information about those studies by the mid-2000’s including in press releases and other publication materials. By 2009, Regeneron had disclosed that VEGF Trap-Eye had

completed Phase 1 and 2 clinical studies and was the subject of Phase 3 clinical studies.

61. Below, I provide a table summarizing Regeneron's VEGF Trap-Eye/aflibercept studies, the dosing regimens that were used in those studies, the specific names given to those studies by Regeneron, and the prior art publications in which those studies were disclosed.

Clinical Study	Study Name	Dosing Regimen	Prior Art
Phase 1 (AMD)	CLEAR-IT 1	Single intravitreal dose (0.5, 2, & 4 mg)	Dixon; Nguyen-2009
Phase 2 (AMD)	CLEAR-IT 2	Monthly or quarterly through week 12 followed by PRN (0.5, 2 & 4 mg)	Dixon; Adis
Phase 3 (AMD)	VIEW 1; VIEW 2	0.5 or 2.0 mg every 4 weeks during the first year. Thereafter as frequently as every 4 weeks, but no less frequently than every 12 weeks. 2.0 mg every 8 weeks (including one additional 2.0 dose at week 4) during the first year. Thereafter, a dose may be	Dixon; Adis; NCT-795; NCT-377; Regeneron (8-May-2008)

		administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.	
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62. Below, I also provide information that was disclosed before the alleged priority date of the '345 patent by Regeneron regarding its clinical trial program for VEGF Trap-Eye/aflibercept in press releases beginning from 2007:

Press Release Date	Representative Disclosure
2007-March-27 Ex. 1019	Phase 2 trial: “a 12-week, multi-center trial” in which “two groups received either 0.5 or 2.0 mg of VEGF Trap-Eye administered every four weeks, and three groups received a single dose of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye” yielding “a statistically significant reduction in retinal thickness after 12 weeks.”
2007-Aug.-02 Ex. 1020	Phase 2 trial: “In an analysis of interim data from the ongoing Phase 2 trial in wet AMD, where patients were treated with the VEGF Trap-Eye either monthly or quarterly, combined data for all patients demonstrated a statistically significant reduction in retinal thickness and improvement in visual acuity after 12weeks, compared to baseline.”
2008-Apr.-28 Ex. 1021	Phase 2 trial: “Two groups initially received monthly doses of 0.5 or 3 milligrams (mg) of VEGF Trap-Eye for 12 weeks and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg ... (at baseline and week 12). Following the initial 12-week fixed dose phase of the trial, patients continued to received therapy at the same dose on a PRN dosing schedule based upon physician assessment of the need for re-treatment in accordance with pre-specified criteria”; “Patients receiving monthly doses of VEGF Trap-Eye, either 5.0 or 2.0 mg, for 12 weeks followed by PRN dosing thereafter achieved mean improvement in acuity of 8.0 (p less than 0.01 versus baseline) an 10.1 letter (p less than -.0001 versus baseline), respectively, and mean decrease in retinal thickness of 141 (p

Press Release Date	Representative Disclosure
	less than .0001 versus baseline) and 162 microns (p less than 0.0001 versus baseline) at week 32, respectively”; “After the last fixed-dose administration at week 12, patients from all dose groups combined required, on average, only one additional injection over the following 20 weeks to maintain the visual acuity gain established during the fixed-dosing period. Notably, 55 percent of the patients who received 2.0 mg monthly for 12 weeks did not require any additional treatment throughout the next 20-week PRN dosing period. Moreover, 97 percent of the patients who received 2.0 mg monthly for 12 weeks did not require re-dosing at the week 16 evaluation visit.” Phase 3 trials (VIEW 1 & 2): “two Phase 3 trials, ... evaluating VEGF Trap-Eye using four- and eight-week dosing intervals in direct comparison with ranibizumab ... administered every four weeks according to its label during the first year of the studies. PRN dosing will be evaluated during the second year of each study.”
2008-May-08 Ex. 1022⁷	Phase 3 trials (VIEW 1 & 2): “Both VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks”; “In the first year, the VIEW 2 ... study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals and 2.0 mg at an 9-week dosing interval, including one additional 2.0 mg dose at week four. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but not more often than every 4 weeks until the end of the study.”
2008-Aug-19	Phase 2 trial: “Patients receiving four monthly doses of VEGF Trap-Eye, either 2.0 or 0.5 mg, for 12 weeks followed by PRN dosing thereafter, achieved mean improvements in

⁷ Regeneron’s development partner, Bayer, also disclosed this information in its own May 8, 2008 press release. Ex. 1032.

Press Release Date	Representative Disclosure
Ex. 1023	visual acuity versus baseline of 9.0 letters ($p < 0.0001$) and 5.4 letters ($p = 0.085$), respectively, and mean decreases in retinal thickness versus baseline of 143 microns ($p < 0.0001$) and 125 microns ($p < 0.0001$) at week 52, respectively. During the subsequent PRN dosing phase, patients initially dosed on a 2.0 mg monthly schedule received, on average, only 1.6 additional injections and those initially dosed on a 0.5 mg monthly schedule received, on average, 2.5 injections.” Phase 3 trials (VIEW 1 & 2): VIEW 1 and 2 are “evaluating VEGF Trap-Eye dosed 0.5 mg every 4 weeks, 2 mg every 4 weeks, or 2 mg every 8 weeks (following three monthly doses) in direct comparison with ranibizumab (Lucentis®, a registered trademark of Genentech, Inc.) administered 0.5 mg every four weeks according to its U.S. label during the first year of the studies. PRN dosing will be evaluated during the second year of each study.”
2008-Sep.-28 Ex 1039	Phase 2 trial: “VEGF Trap-Eye achieved durable improvements in visual acuity and in biologic measures of neovascular disease, including retinal thickness and active choroidal neovascularization lesion size, for up to one year in a Phase 2 study in the neovascular form of Age-related Macular Degeneration (wet AMD).” Phase 3 trials (VIEW 1 & 2): “Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12). Following the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment in accordance with pre-specified criteria. Patients were monitored for safety, retinal thickness, and visual acuity.”
2009-Sep.-14 Ex. 1040	Phase 3 trials (VIEW 1 & 2): “In the first year of the studies, the safety and efficacy of VEGF Trap-Eye at doses of 0.5 mg and 2.0 mg administered at four-week intervals and 2.0 mg at an eight-week dosing interval following one additional 2.0 mg dose at week four are being evaluated. Patients randomized to the ranibizumab arm of the trial will receive a

Press Release Date	Representative Disclosure
	0.5 mg dose every four weeks. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended PRN regimen with a dose administered at least every 12 weeks, but not more often than every four weeks until the end of the study.”
2010-Feb-2010	Phase 2 trial (DA VINCI): “219 patients with clinically significant DME with central macular involvement were randomized to five groups”; “Two groups received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye through the 6 month dosing period. Two groups received three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by either every 8-week dosing or as needed (PRN) dosing with specific repeat dosing criteria”; “The ability of VEGF Trap-Eye to significantly improve vision in patients with DME in this initial Phase 2 study is encouraging.”

IX. THE '345 PATENT

63. I have reviewed and analyzed the '345 patent, which is titled “Use of VEGF Antagonist to Treat Angiogenic Eye Disorders,” including the issued claims, specification and prosecution history. The '345 patent issued on November 10, 2020 from Application No. 16/159,282 (“the '282 application”), filed on October 12, 2018. On its face, the '345 patent is assigned to Regeneron Pharmaceuticals, Inc., and names George D. Yancopoulos as the sole inventor.

A. Priority Date

64. I have been asked to assume, for purposes of my analysis and coming to my opinions, that the priority date of the '345 patent is November 21, 2011.

B. Challenged Claims

65. The Challenged Claims are generally directed to “[a] method of treating an angiogenic eye disorder in a patient,” including AMD, DR, and DME via administering approximately 2 mg or 5 mg aflibercept every four weeks for the first 3 months, followed by continuing to administer approximately 2 mg or 5 mg aflibercept once every 12 weeks.

66. The Challenged Claims are reproduced in their entirety below:

1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.

2. The method of claim 1, wherein the VEGF antagonist is aflibercept.

3. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

4. The method of claim 3, wherein the intraocular administration is intravitreal administration.

5. The method of claim 4, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

6. The method of claim 5, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

7. The method of claim 5, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

8. The method of claim 5, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

9. The method of claim 8, wherein the angiogenic eye disorder is age related macular degeneration.

10. The method of claim 8, wherein the angiogenic eye disorder is diabetic retinopathy.

11. The method of claim 8, wherein the angiogenic eye disorder is diabetic macular edema.

C. Prosecution History

67. The '345 patent was filed as the '282 application on October 12, 2018, seeking approval of 20 pending claims, including one independent claim, which recited:

A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF

antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose.

68. Thereafter, applicants filed an amendment cancelling pending claims 1-20 and adding new pending claims 21-42. Ex. 1002 at 401-405, Oct. 12, 2018 Preliminary Amendment.

69. In April 2019, the examiner rejected the pending claims over claims 1-5 of the '746 patent; claims 1-6 of the '747 patent; claims 1-11 of the '799 patent; claims 1-15 of the '049 patent; claims 1-26 of the '338 patent; claims 1-12 of the '069 patent; and claims 1-12 of the '681 patent. *Id.*, 2019.04.03 Office Action at 2. The examiner noted that though some of the double patenting references “d[o] not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosages and dosage schedules.” *Id.*, Mar. 29, 2019 Office Action at 341-345. The examiner also noted that SEQ ID NO: 16 disclosed in the '746 patent; SEQ ID NO:6 disclosed in the '747 and '799 patents; SEQ ID NO:23 disclosed in the '049 patent; and SEQ ID NO:2 disclosed in the '338, '681 and '069 patents “comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component.” *Id.*

70. A third-party submission was filed on May 28, 2019, in which the Dixon reference was identified and a claim chart comparing disclosures from Dixon and pending claims 21-31 were submitted. *Id.* at 331-333, May 28, 2019 Third Party Submission. The Third-Party Submission also identified a September 14, 2009 press release titled “Enrollment Completed in Regeneron and Bayer HealthCare Two Phase 3 Studies of VEGF Trap-EYE in Neovascular Age-Related Macular Degeneration (Wet AMD)” (“Regeneron 2009”) and a claim chart comparing disclosures from Regeneron 2009 and pending claims 32-42 were submitted. *Id.* Applicants were notified of the third-party submission on May 31, 2019. *Id.* at 322, May 31, 2019 Miscellaneous Communication to Applicant.

71. In June 2019, the applicant responded to the examiner’s non-final rejection. *Id.* at 298-305, June 28, 2019 Resp. to Office Action. Citing to Heier, applicants asserted that at the time of the invention, standard of care for AMD was injection of ranibizumab into the eye once per month and that this treatment was (i) expensive, (ii) painful to the patient, (iii) inconvenient for the patient and their family, (iv) psychologically and physically traumatic, and (v) subjected the patient to potential adverse effects with each administration. *Id.* at 300. As such, the applicants argued, “there was a need in the art for alternative treatment protocols.” *Id.* The applicant further argued that there are virtually an infinite number of different treatment protocols that could be tested and therefore “the claimed

treatment protocol is [not] *prima facie* obvious in view of the prior art standard of care.” *Id.* Further, applicant pointed to the Heier reference and working examples of the specification to assert the secondary considerations of improved unexpected results. According to the applicant, the Heier paper showed that it is possible to treat angiogenic eye disorders such as AMD in over 2400 patients who were administered “VEGF receptor-based chimeric molecule known as aflibercept or ‘VEGF Trap’” according to the claimed treatment protocol—e.g., less frequently than monthly dosing. *Id.* at 301-303, June 28, 2019 Resp. to Office Action.

72. Thereafter, the applicants filed a supplemental amendment pursuant to which pending claims 21 and 32 were amended to clarify the VEGF receptor as Flt1 and claims 23 and 34 were amended to correct an error in claim dependency. *Id.* at 279-289, Aug. 14, 2019 Resp. to Office Action. The applicant also reiterated its responses from its June 28, 2019 Response to the April 2019 Office Action. The day after submitting its supplemental amendment, applicants filed another supplemental amendment pursuant to which claims 28 and 29 were amended to correct a further error in claim dependency. *Id.* at 270, Aug. 15, 2019 Resp. to Office Action.

73. In October 2019, the examiner issued another non-final rejection for all pending claims. *Id.* Oct. 1, 2019 Office Action at 2. The examiner rejected pending claims 21-31 as anticipated by Dixon. *Id.* at 3. The examiner explained that

Dixon et al. teaches methods for treating an angiogenic eye disorder, including age-related macular degeneration,

diabetic retinopathy, and diabetic macular edema (See §2.6.1 and 2.6.2 at pp. 3-4) with the VEGF antagonist aflibercept. Dixon et al. teaches that patients received intraocular/intravitreal monthly doses of 0.5mg or 2mg for 12 weeks (0, 4, 8, 12) followed by treatment of the same dose on a PRN basis. Therefore, Dixon et al. teaches a treatment protocol of (1) a single dose of 0.5mg or 2mg at week 0, followed by 3 secondary doses in 4-week intervals (week 4, 8 and 12); followed by tertiary doses on a PRN basis. Dixon et al. further teaches criteria for PRN basis, including visual (ETDRS letters) or anatomical (retinal thickness by OCT) outcomes (See §2.6.2 at pg. 1576). The VEGF antagonist disclosed by Dixon et al. is aflibercept, a VEGF trap which comprises immunoglobulin-like (Ig) domain 2 of Fltl, Ig domain of 3 Flkl, and IgG Fc fragment as a multimerizing component (See §2.2 and §2.3 at pg. 3).

Id. at 3-4. The examiner rejected pending claims 32-42 as anticipated by Regeneron 2009:

Regeneron teaches methods for treating an angiogenic eye disorder, including neovascular age-related macular degeneration with the VEGF antagonist VEGF-Trap-Eye. Regeneron also teaches VEGF Trap Eye for the treatment of diabetic macular edema and central retinal vein occlusion (See pg. 1). Regeneron teaches that patients received intraocular/intravitreal doses of 0.5mg or 2g VEGF Tap-Eye at 4-week intervals in the first year, followed by continual treatment for another year on a flexible, PRN regiment, with a dose administered at least every 12 weeks, but not more often than every 4 weeks. Therefore, Regeneron teaches treatment of AMD patients with (1) a single dose of 0.5mg or 2mg, followed by (2) secondary doses at 4-week intervals for a year, followed by (3) treatment for another year based on a flexible PRN schedule, which would include at least one tertiary dose at 12 weeks from the immediately preceding dose. The VEGF antagonist disclosed by Regeneron is VEGF Trap-

Eye, which is a VEGF trap which is a VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor. As disclosed in Dixon et al. (referenced *supra*), VEGF Trap Eye comprises immunoglobulin-like (IG) domain 2 of Fltl, Ig domain 3 of Flkl, and IgG Fc fragment as a multimerizing component (See §2.2 and §2.3 at pg. 3).

Id. at 4-5.

74. In January 2020, the applicant responded to the Office Action and amended pending claim 21 to add

wherein the angiogenic disorder is age-related macular degeneration, retinal vein occlusion (RVO), central retinal vein occlusion, macular edema following CRVO, branch retinal vein occlusion (BRVO), diabetic macular edema (DME), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreous neovascularization, pannus, pterygium, vascular retinopathy or diabetic retinopathy.

Id. at 2.

75. Applicant also asserted that Dixon did not disclose each limitation of the pending claims because Section 2.6.1 of Dixon did not relate to PRN dosing but instead discussed a Phase I trial of intravenous aflibercept and a trial wherein the first part was a sequential cohort dose escalation study and the second part was a single intravitreal injection of either 0.4 or 4 mg of VEGF Trap-Eye. *Id.* at 6. Applicant further asserted that Section 2.6.2 of Dixon disclosed treatment of subfoveal choroidal neovascularization and

did not disclose treatment of age-related macular degeneration, retinal vein occlusion, macular edema following CRVO, branch retinal vein occlusion (BRVO), diabetic macular edema (DME), 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 or diabetic retinopathy.

Id. at 6. I note that the examiner’s reliance on Dixon as invalidating prior art differs from my reliance on that reference. For example, in addition to Dixon, ***my analysis below also takes into account the disclosures in NCT-377 that were incorporated into Dixon. In contrast, the examiner did not consider NCT-377.***

76. Applicant further asserted that Regeneron 2009 does not disclose tertiary dosing administered 12 weeks after the immediately preceding dose and that dosing component was not inherently disclosed either because it only disclosed that “a dose interval may extend out as far as 12 weeks.” *Id.* at 6-7.

77. In March 2020, applicant filed supplemental amendments and additional arguments and remarks. Specifically, applicant cancelled pending claims 21-31 stating that it would “pursue subject matter encompassed by these claims within a yet to be filed application.” *Id.* Mar. 16, 2020 Resp. to Office Action at 4. Applicant also provided a summary for an examiner interview that took place March 6, 2020. *Id.* “During the interview, the Examiner requested further clarification with respect to specific claim elements of the pending independent claims with respect to

[Regeneron 2009] having an indicated date of September 13, 2009.” *Id.* In response, applicant argued that Regeneron 2009 had not yet been shown to be prior art even though it has a displayed date of September 14, 2009. I understand from counsel that the applicant’s representation to the examiner that Regeneron 2009 was not published before the alleged priority date of the ’345 patent was the basis for a claim of inequitable conduct in district court proceeding.

78. Applicant further argued that Regeneron 2009 provided a “[m]ere mention of a prospective possibility of dosing at 12 weeks [that] does not specifically indicate or teach towards a method where 12-week dosing would be undertaken, let alone successful.” *Id.* at 5. I understand from counsel that this argument has already been considered and rejected by the PTAB in IPR proceedings for claims that are substantively similar to the Challenged Claims recited in patents from the same patent family as the ’345 patent.

79. An Issue Notification was filed October 2020, identifying the “Issue Date” as November 10, 2028.

80. In March 2022, applicant filed a Request for Certificate of Correction, correcting column 13, line 5; column 15, lines 9-10; and column 15, line 12 from “gained ≤ 15 ETDRS” to “gained ≥ 15 ETDRS”. *Id.*, 2022.03.04 Request for Cert of Correction at 1.

X. SCOPE OF PRIOR ART

A. “Sharp” (Ex. 1024) – Patrick S. Sharp, *The Role of Growth Factors in the Development of Diabetic Retinopathy*. *Metabolism*, Vol. 44, No. 10, Suppl 4 (October 1995).

81. Sharp is an article that was published in October 1995, which is more than one year before the earliest priority date of the '345 patent. Therefore, I understand that it qualifies as prior art.

82. Sharp discloses that “Proliferation of retinal blood vessels is one of the most striking features of advanced diabetic retinopathy. This feature has led to the conclusion that the normal balance of growth factors, which usually serves to keep angiogenesis in check, is disturbed in diabetic retinopathy.” Ex. 1024 at 1; *id.* (“Proliferative diabetic retinopathy is one of the few examples of human pathological conditions in which abnormal growth of new vessels is one of the primary features.”).

83. Sharp further discloses that “[p]erhaps more promising as the angiogenic factor of diabetic retinopathy is the family of vascular endothelial cell growth factors (VEGFs), of which four have been identified.” *Id.* at 2. Sharp teaches that “[i]n the context of diabetic retinopathy, [VEGF] [is] upregulated by hypoxia” and that “VEGF has been reported to be present in increased amounts in the aqueous and vitreous of patients with all grades of diabetic retinopathy, particularly those with proliferative disease.” *Id.*

B. “Holash” (Ex. 1005) - Jocelyn Holash et al., VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects, 99 PROC. NAT’L ACAD. SCI. 11393 (2002)

84. Holash is an article that was published in April 2002, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that it qualifies as prior art.

85. Holash teaches that “[t]he sprouting of new blood vessels, termed angiogenesis, is required to support growth in the embryo and young animals ... [h]owever, aberrant angiogenesis is also associated with a number of pathological conditions and diseases.” Ex. 1005 at 1. “Consequently, much effort has been directed toward discovering antiangiogenic agents and evaluating them.” *Id.* Holash asserts that “the best characterized and most highly validated antiangiogenic approaches involves targeting the vascular endothelial growth factor (VEGF) pathway” as that is “the only well-defined signaling pathway known to be required for normal development of the vasculature as well as for the pathologic angiogenesis that accompanies cancer and other disease states.” *Id.*

86. Holash explains that “[t]he VEGF pathway is initiated when VEGF binds to its receptors on endothelial cells. The two best characterized VEGF receptors are termed VEGF receptor 1 (VEGFR1) and VEGF receptor 2 (VEGFR2).” *Id.* Holash also teaches that “blockade of the VEGF pathway has been achieved by many different means” but that “one of the most effective ways to block the VEGF

signaling pathway is to prevent VEGF from binding to its normal receptors by administering decoy VEGF receptors” and that “[t]he highest-affinity VEGF blocker described to date is a soluble decoy receptor created by fusing the first three Ig domains of VEGFR1 to the constant region (Fc portion) of human IgG1.” *Id.*

87. Holash goes on to “describe the engineering of anti-VEGF agent, termed VEGF-TRAP_{R1R2}.” EX. 1005 at 5. Holash discloses that “VEGF-Trap_{R1R2} was created by fusing a second Ig domain of VEGFR1 with the third Ig domain of VEGFR2.” *Id.* at 1-2.

88. Holash further discloses that “VEGF-Trap_{R1R2} [c]ompare[s] [f]avorably with [a]ntibodies [t]argeting VEGFR2.” *Id.* at 15.

C. “Rudge” (Ex. 1032) – J.S. Rudge et al., VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene®-Based Discovery of the Next Generation of Angiogenesis Targets, 70 COLD SPRING HARBOR SYMPOSIA QUANTITATIVE BIOLOGY 411 (2005)

89. Rudge was published in 2005, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Rudge qualifies as prior art.

90. Rudge discloses that “[i]n addition to the promise of anti-VEGF approaches in cancer, blocking VEGF-A has also been impressive in maintaining and improving vision in wet age related macular degeneration (AMD), a disease marked by leaky and proliferating vessels which distort the retina, and these data

suggest that VEGF blockade may provide benefit in other eye diseases involving vascular leak and proliferation.” Ex. 1032 at 1.

91. Rudge “focus[es] on the development and status of a novel VEGF-blocking agent, termed the VEGF Trap, that retains many of the advantages of a blocking antibody but may offer further potential.” *Id.* Rudge explains that “[w]e decided to exploit our Trap technology platform (Economides et al. 2003), which involves defining and fusing minimal binding units from different receptor components to generate chimeric fusion proteins that act as high-affinity soluble blockers, in an attempt to create a potent and well-behaved Trap for VEGF. The result was a chimeric fusion protein containing a modified domain 2 of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc region of human IgG1, resulting in a fully human protein that we term VEGF Trap (Holash et al. 2002).” *Id.* at 3.

92. Rudge teaches that “VEGF Trap also displays extended pharmacological half-life, allowing long-term as well as very high affinity blockade. The VEGF Trap has performed impressively in extensive animal studies of cancer and eye diseases, and initial clinical trials appear promising.” *Id.* at 1.

93. Rudge discloses that “[i]nitial clinical studies in human patients suffering from both AMD and diabetic edema and retinopathy appear quite promising, with evidence in early trials that the VEGF Trap can rapidly and

impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity (Nguyen et al. 2006; Shah et al. 2006).” *Id.* at 4-5.

D. “Bashshur” (Ex. 1028) - Ziad F. Bashshur et al., Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration, 142 AM. J. OPHTHALMOLOGY 1 (2006)

94. Bashshur was published in 2006, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Bashshur qualifies as prior art.

95. Bashshur teaches “Age-related macular degeneration (AMD) is a leading cause of legal blindness in the industrialized world. Although neovascular AMD is less prevalent than atrophic AMD, it accounts for most cases with severe visual loss from AMD. Vascular endothelial growth factor (VEGF) has been implicated in the choroidal neovascularization (CNV) of AMD. VEGF helps promote endothelial cell growth and increases vascular permeability.” Ex. 1028 at 1.

96. Bashshur discloses that “intravitreal injections pose several potential risks, including endophthalmitis, vitreous hemorrhage, and retinal detachment” and that “[i]ntravitreal bevacizumab itself may cause inflammation or ocular toxicity with repeated injections.” *Id.* at 7-8.

E. “Nguyen-2006” (Ex. 1033) - Quan Dong Nguyen et al., A Phase I Trial of an IV-Administered Vascular Endothelial Growth Factor Trap for Treatment in Patients with Choroidal Neovascularization

due to Age-Related Macular Degeneration, 113
OPHTHALMOLOGY 1522 (2006)

97. Nguyen-2006 was published in 2006, which is more than one year before the earliest priority date of the '345 patent. Therefore, I understand that Nguyen-2006 qualifies as prior art.

98. Nguyen-2006 reports the results from the Phase I (CLEAR-IT 1) study in which the safety, pharmacokinetics, and biological activity of intravenous administration of VEGF Trap was assessed. Ex. 1033 at 1.

99. Nguyen-2006 explains that “VEGF Trap is a recombinant soluble VEGF receptor protein in which the binding domains of VEGF receptors 1 and 2 are combined with the Fc portion of immunoglobulin G.” *Id.* at 2.

100. Nguyen-2006 discloses the Phase I study design included three dose levels of VEGF: 0.3, 1.0, and 3.0 mg/kg. *Id.* at 3. “In each cohort, subjects were randomized in a 3:1 ratio (drug: placebo). After enrollment in the 0.3-mg/kg cohort was completed, there was a 2-week waiting period before the 1.0-mg/kg cohort was begun. There was also a 2-week waiting period after the 1.0-mg/kg cohort was enrolled before enrollment of the 3.0-mg/kg cohort was begun.” *Id.*

101. Nguyen reports that

[e]very patient treated with 1.0-mg/kg VEGF Trap had reduction in foveal thickness 2 weeks after the first infusion. At day 71, 2 weeks after the fourth infusion, the median reduction in excess foveal thickness was 80%, a dramatic difference from placebo-treated patients, who

had no reduction in excess foveal thickness. Similar dramatic reductions in excess total macular volume were seen after infusions of 1.0-mg/kg VEGF Trap. These effects were sustained for at least 2 weeks, but not 1 month, after a single infusion of 1.0 mg/kg, whereas the limited data available for patients treated with 3.0-mg/kg VEGF Trap suggest a sustained effect for at least 1 month. This difference in duration of effect is explainable by the pharmacokinetics of VEGF Trap, because active VEGF Trap was still detectable in patient plasma 1 month after infusion of 3.0 mg/kg, but not 1.0 mg/kg. Six weeks after a fourth 1.0-mg/kg infusion, the median excess foveal thickness was 40%, suggesting loss of about half of the maximal treatment effect; therefore, repeated infusions of 1.0-mg/kg VEG Trap may be needed to maintain benefits.

Id. at 9.

F. “Rudge-2007” (Ex. 1034) - John S. Rudge et al., VEGF Trap Complex Formation Measures Production Rates of VEGF, *Providing a Biomarker for Predicting Efficacious Angiogenic Blockade*, 104 PNAS 18363 (2007)

102. Rudge-2007 was published in 2007, which is more than one year before the earliest priority date of the '345 patent. Therefore, I understand that Rudge-2007 qualifies as prior art.

103. George D. Yancopoulos, who is the named inventor on the face of the '345 patent is identified as a contributor for the Rudge-2007 article. Ex. 1034 at 1 (“Contributed by George D. Yancopoulos. September 17, 2007”).

104. Rudge-2007 discloses that “VEGF Trap is a fully human soluble decoy receptor protein that consists of a fusion of the second Ig domain of human VEGF receptor (VEGFR) 1 and the third Ig domain of human VEGFR2 with the constant

region (Fc) of human Ig IgG1.” *Id.* Notably, in support of this statement, Rudge-2007 cites to the Holash article (Ex. 1005), that I discuss above.

105. Rudge-2007 explains that studies “suggest[] that VEGF Trap might behave very differently than VEGF antibodies, because antibodies ... rapidly are cleared from the circulation.” *Id.* at 3.

G. “Heimann-2007” (Ex. 1042) – Heinrich Heimann, *Intravitreal Injections: Techniques and Sequelae*. Frank G. Holz, Richard F. Spaide, MEDICAL RETINA. Springer. (2007) 67-87.

106. Heimann-2007 is a chapter titled “Intravitreal Injections: Techniques and Sequelae” that appears in the book “Medical Retina” published in 2007, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Heimann-2007 qualifies as prior art.

107. Heimann-2007 teaches that “[b]acterial infections of the anterior segment and ocular adnexia increase the risk of endophthalmitis and should be treated before performing an intravitreal injection.” And that pre-operation assessments be done “to rule out possible contraindications .. that might complicate the injection.” Ex. 1042 at 17; *id.* at 21 (“[e]xclude patients with suspected bacterial infections or the anterior segment (e.g., blepharitis, conjunctivitis).”). Heimann-2007 further instructs that “preparation of the ocular surface should aim to minimize bacterial contamination during the injection.” *Id.* at 12.

108. Heimann-2007 discloses that “[e]ndophthalmitis is the most feared complication of intravitreal injections,” (*id.* at 67), due to its “potentially devastating consequences.” *Id.* Heimann-2007 further discloses that endophthalmitis prevention is “one of the key issues” regarding intravitreal injections. *Id.* Heimann-2007 also discloses that “severe intraocular inflammatory reactions can be seen” following intravitreal injections, and notes that it can be “extremely difficult, to differentiate a sterile inflammatory process from an inflammatory reaction associated with infectious endophthalmitis.” *Id.* at 11.

H. “Brown” (Ex. 1025) - David M. Brown & Carl D. Regillo, Anti-VEGF Agents in the Treatment of Neovascular Age-Related Macular Degeneration: Applying Clinical Trial Results to the Treatment of Everyday Patients, 144 AM. J. OPHTHALMOLOGY 627 (2007)

109. Brown was published in 2007, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Brown qualifies as prior art.

110. Brown explains that “[n]eovascular AMD is associated with increased vascular permeability as well as CNV infiltration” which “leads to abnormal fluid collection within or below the retina that causes visual dysfunction when it involves the center of the macula.” Ex. 1025 at 1.

111. Brown goes on to discuss anti-VEGF treatments and discloses that clinical trials “provide clear evidence that monthly ranibizumab is safe and effective

for the treatment of neovascular AMD. However, many clinicians and patients are reluctant to commit to a strategy of 24 [intravitreal] injections in the first two years of treatment.” *Id.* at 8. Brown explain “[t]he ocular risk of anti-VEGF injections appear to be primarily related to the injection process itself” and “[b]ecause of both ocular and systemic safety concerns, as well as cost and physician and patient convenience issues, ideally an alternative dosing strategy can be used to decrease the number of required injections for anti-VEGF agents.” *Id.* at 630. Brown further teaches that “[p]harmacotheapeutics that inhibit VEGF-A with a longer duration of action than ranibizumab or that can be incorporated in sustained-release delivery systems may be available in the near future.” *Id.* at 10.

I. “The 058 application” (Ex. 1043) – U.S. Published Patent Application (2007)

112. The 058 application was published August 16, 2007, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that the 058 application qualifies as prior art.

113. The 058 application discloses that “[a]ngiogenesis is implicated in the pathogenesis of intraocular neovascular diseases” (Ex. 1043 at [0003]), which it defines as “a disease characterized by ocular neovascularization, Examples of intraocular diseases, include, but are not limited to, e.g., proliferative retinopathies, choroidal neovascularization (CNV), [AMD], diabetic and other ischemia-related retinopathies, [DME], pathological myopia, von Hippel-Lindau disease,

histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, etc.” *Id.* at [0074].

114. The 058 application further discloses that “the concentration of VEGF in eye fluids are highly correlated to the presence of active proliferation of blood vessels in patients with diabetic and other ischemia-related retinopathies.” *Id.* at [0008].

115. The 058 application also discloses “[a] method for treating intraocular neovascular disease, comprising: administering to a mammal a number of first individual doses of an VEGF antagonist; followed by administering to the mammal a number of second individual doses of the antagonist, wherein the second individual doses are administered less frequently than the first individual doses.” *Id.* at claim 21.

J. “Fung” (Ex. 1045) – Anne F. Fung, et al., An Optical Coherence Tomography-Guided, Variable Dosing Regimen with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration. Am J Ophthalmol (2007) 143:566-583

116. Fung was published in 2007, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Fung qualifies as prior art.

117. Fung discloses “[i]nhibition of vascular endothelial growth factor-A (VEGF) is an effective strategy for the treatment of neovascular age-related macular degeneration (AMD).” Ex. 1045 at 1.

118. Fung further discloses that though “[t]he most effective treatment uses ranibizumab (Lucentis, Genentech Inc. ...)[,]” “most of the [Phase I/II] study participants enrolled in an open-label extension study to evaluate the safety and tolerability of long-term (up to four years) continued treatment with intravitreal injection.” *Id.* at 566-567. Fung further disclosed that “[a] decrease in the number of injections would reduce the potential risk of injection-related complications, and an increase in the injection-free interval would reduce the burden of frequent follow-up evaluations.” *Id.* at 16-17.

K. “Rudge-2008” (Ex. 1035) - John S. Rudge et al., CLINICAL DEVELOPMENT OF VEGF TRAP, IN ANGIOGENESIS (William D. Figg & Judah Folkman eds. 2008)

119. Rudge-2008 was published in 2008, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Rudge-2008 qualifies as prior art.

120. Rudge-2008 identifies, as one of the authors, George D. Yancopoulos, who is also the named inventor on the face of the ’345 patent. Ex. 1035 at 3.

121. Rudge-2008 discloses that “Angiogenesis is a vital process not only during development, but also in the adult in settings of wound repair and reproduction [1, 2]. However, in diseases characterized by uncontrolled, pathological angiogenesis, such as solid tumors or vascular diseases of the eye, inhibition of angiogenesis would be of therapeutic benefit.” *Id.*

122. Rudge-2008 teaches that “a clear consensus is emerging that a single growth factor, VEGF is the critical requisite driver of both physiological and pathological angiogenesis in most settings” and that “[r]ecent clinical studies have validated VEGF as a bona fide target for therapeutic intervention in cancer as well as in vascular diseases affecting the eye, such as wet AMD.” *Id.*

123. Rudge-2008 discloses that

[VEGF Trap] was designed to bind VEGF with exceedingly high-affinity. The VEGF Trap is a soluble chimeric receptor in which key domains of VEGFR1 (domain 2) and VEGFR2 (domain 3) are fused to the constant region (Fc portion) of human IgG1 [34]. This fully human protein is capable of binding all isoforms of VEGF-A with very high affinity ($K_D < 0.5$ pM for hVEGF165). Moreover, and in contrast to antibodies directed against VEGF-A, the VEGF Trap also binds PlGF, a VEGF family member also implicated in pathological angiogenesis [46] ($K_D \sim 25$ pM for hPlGF2).

Id. at 4.

124. Rudge-2008 further discloses that “In addition, the VEGF Trap was engineered to exhibit excellent pharmacokinetic properties, and has a circulating half-life in humans of approximately 2–3 weeks, allowing for bi-weekly or even less frequent dosing.” *Id.*

125. Rudge-2008 further discloses that “[t]he promising results in preclinical models supported the introduction of VEGF Trap into the clinic for treatment of both

wet AMD and diabetic macular edema, using a version of VEGF Trap specifically formulated for intra-ocular administration, termed VEGF Trap-Eye.” *Id.* at 5-6.

126. Rudge-2008 describes a Phase 2 trial in which “VEGF Trap-Eye was given at monthly intervals at doses of 0.5 or 2.0 mg, or as a single injection of 0.5, 2.0 or 4.0 mg. In the interim analysis, VEGF Trap-Eye met the pre-specified primary endpoint of reducing retinal thickness as measured by ocular coherence tomography (OCT) at 12 weeks compared with baseline (all groups combined, decrease of 135 μm , $P < 0.0001$).” *Id.* at 6.

127. Rudge-2008 further discloses that “[i]n addition, as reported at ARVO 2007 [60,65], a Phase 1 study of VEGF Trap-Eye in diabetic macular edema (DME) showed that a single intravitreal injection in patients with longstanding diabetes resulted in a marked decrease in mean central retinal thickness and mean macular volume throughout the 6 week observation period.” *Id.*

**L. NCT-795 (Ex. 1017) - Degeneration (AMD) (VIEW1),
NCT00509795, ClinicalTrials.gov (Apr. 28, 2009),
<https://clinicaltrials.gov/ct2/show/NCT00509795>**

128. NCT-795 is an online record for the VIEW 1 clinical trial NCT-00509795 from the clinicaltrials.gov cite, which is a database of clinical trial information developed by the National Library of Medicine and a service of the U.S. National Institutes of Health.

1. NCT-795 qualifies as prior art.

129. ClinicalTrials.gov is a publicly available website that is accessible to anyone without any login requirements or other credentials and discloses information about clinical trial being conducted in the United States and abroad:

ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions. NIH and the Food and Drug Administration (FDA) worked together to develop the site, which was made available to the public in February 2000.

Physicians, patients, and researchers can readily access the information published on the website. As such POSA's would have access to the clinical study information disclosed on the website. In fact, I have personally used the clinicaltrial.gov website to research and review information about clinical studies over the course of my professional career. I am also aware that many of my peers routinely use the clinicaltrials.gov website for similar purposes.

130. I understand that U.S. federal law requires clinical study sponsors or investigators to submit information about clinical studies they are intending to or currently performing to the clinicaltrials.gov website. After clinical study information is submitted or "Released" by the submitter and passes review by ClinicalTrials.gov staff, a NCT Number also known as the ClinicalTrials.gov Identifier is assigned.

131. I also understand that the law requires sponsors or investigators to update the submitted clinical study information, including with respect to any

amendments to the study description, study design, arms and interventions and other substantive information. I am aware that clinicaltrial.gov maintains an archive site, found at the link “History of Changes”:

Responsible Party:	Regeneron Pharmaceuticals
ClinicalTrials.gov Identifier:	NCT00509795 History of Changes
Other Study ID Numbers:	VGFT-OD-0605
First Posted:	August 1, 2007 Key Record Dates
Results First Posted:	April 16, 2012
Last Update Posted:	December 28, 2012
Last Verified:	December 2012

Utilizing the “History of Changes” archive, the public may identify what updates have been made to the clinical study and the date on which the update occurred, along with a comparison showing changes that were made since the previous update. A partial snapshot of this portion of the “History of Changes” page is shown here:

1/7/2021

History of Changes for Study: NCT00509795

Version	A	B	Submitted Date	Changes
3	☐	☐	November 14, 2007	Contacts/Locations and Study Status
4	☐	☐	December 4, 2007	Study Status and Contacts/Locations
5	☐	☐	March 13, 2008	Study Status and Eligibility
6	☐	☐	June 26, 2008	Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification
7	☐	☐	January 22, 2009	Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators
8	☒	☐	March 3, 2009	Study Status and Contacts/Locations
9	☐	☒	April 28, 2009	Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification

Ex. 1017 at 2.

132. Using the above image as an example, the “Version” column identifies the number of updates to the clinical study that have been submitted; the “Submitted Date” column indicates the date on which the updated information was provided to ClinicalTrials.gov and this the date on or about which the information was publicly accessible from the database; and the “Changes” column identifies what portion of the clinical study was updated. Further, one can compare the different versions of the clinical study by selecting from columns “A” and “B.” In this way, one can identify the information that was publicly available on a given date and also how that information differs from information that was disclosed in a previous version. And this is in fact, what I did with respect to NCT-795.

133. The earliest version of NCT-795 submitted to ClinicalTrial.gov was July 31, 2007. *Id.* at 1. It was updated several times such that there are 18 “Versions” that may be accessed from the ClinicalTrials.gov archive. In coming to my opinions in this case, I relied on Version 9, which was published April 28, 2009. *Id.* at 2. Thus, my discussion of NCT-795 going forward is with regards to the version that was available on April 28, 2009, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that NCT-795 qualifies as prior art.

2. Disclosures of NCT-795

134. NCT-795 discloses information about a clinical study with a “Brief Title”: “Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1).” *Id.* at 3. NCT-795 discloses that “[t]his study is a phase III, double masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the US and Canada.” *Id.* at 4.

135. NCT-795 discloses that there are 4 treatment arms for the study and the specific dosing regimens for each VIEW1 treatment arm. *Id.* at 5-8. Specifically, it discloses that patients will be randomly assigned to one of the following four treatment regimens:

- 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
- 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.
- 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be

administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

- 0.5 mg ranibizumab administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.

Id. at 5-7.

136. NCT-795 discloses that the primary outcome measure will be “[t]he proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e., prevention of moderate vision loss).” *Id.* at 9. NCT-795 also notes that the timeframe for assessment will be “Week 52.” *Id.*

M. NCT-377 (Ex. 1018) - VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2), NCT00637377, ClinicalTrials.gov (August 4, 2008), <https://clinicaltrials.gov/study/NCT00637377?id=NCT00637377&rank=1&tab=history&a=4#version-content-panel>

137. NCT-377 is an online record for the VIEW2 clinical trial NCT-00637377 that was publicly available as of August 4, 2008 from the clinicaltrials.gov cite, which is a database of clinical trial information developed by the National Library of Medicine and a service of the U.S. National Institutes of Health.

1. NCT-377 qualifies as prior art.

138. As I have discussed above with respect to NCT-795, ClinicalTrials.gov is a publicly available website that is accessible to anyone without any login requirements or other credentials and discloses information about clinical trials being conducted in the United States and abroad. As such POSA's would have access to the clinical study information disclosed on the website.

139. Utilizing the "Record History" tab, the public may identify what updates have been made to the clinical study and the date on which the update was posted. Ex. 1017 at 1.

140. The earliest version of NCT-377 submitted to ClinicalTrial.gov was March 17, 2008. *Id.* at 1. It was updated several times such that there are 30 "Versions" that may be accessed from the ClinicalTrials.gov archive. In coming to my opinions in this case, I relied on Version 4, which was posted/published August 4, 2008:

First Posted
2008-03-18 [Estimated]
Last Update Submitted that Met QC Criteria
2008-08-04
Last Update Posted
2008-08-05 [Estimated]

Id. at 6. Thus, my discussion of NCT-377 going forward is with regards to the version that was publicly available as of August 8, 2008, which is more than one year before the earliest priority date of the '345 patent. Therefore, I understand that NCT-377 qualifies as prior art.

2. Disclosures of NCT-377

141. NCT-377 discloses information about a clinical study titled “VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2).” *Id.* at 1. NCT-377 discloses that “[t]his study is a phase III, double masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration. Approximately 1200 patients will be randomized in the Europe, Asia, Japan, Australia, and South America.” *Id.* at 7.

142. NCT-377 discloses that there are 4 treatment arms for the study and the specific dosing regimens for each VIEW 2 treatment arm. *Id.* at 8. Specifically, it discloses that patients will be randomly assigned to one of the following four treatment regimens:

- 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. *Id.* at 8-9

- 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. *Id.* at 9.
- 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. *Id.* at 8.
- 0.5 mg ranibizumab administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. *Id.* at 9.

143. NCT-377 discloses that the primary outcome measure will be “[t]he proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e., prevention of moderate vision loss).” *Id.*

N. “Dixon” (Ex. 1007) - James A Dixon et al., VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration, 18 EXPERT OPINION ON INVESTIGATIONAL DRUGS 1573 (2009)

144. Dixon is an article titled “VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration” published in a peer reviewed journal in 2009, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that it qualifies as prior art.

145. Dixon provided background information regarding AMD. Specifically, it disclosed that AMD “affects > 14 million individuals worldwide” and that “neovascular AMD accounts for the vast majority of patients who develop legal blindness.” Ex. 1007 at 1. Dixon further explains that though “few treatment options existed for treatment of neovascular AMD[,] [t]he advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD” and identifies “ranibizumab and bevacizumab as “two anti-VEGF drugs currently in widespread use.” *Id.*

146. Dixon discloses that “[o]ne promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2.” *Id.* Dixon goes on “[t]o review the current literature and clinical trial data regarding VEGF Trap-Eye for the treatment of neovascular-AMD” based on a “[l]iterature review” and concludes that “VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD. Two Phase III clinical trials (VIEW-1 and VIEW-2) comparing VEGF Trap-Eye to ranibizumab are currently continuing and will provide vital insight into the clinical applicability of this drug.” *Id.*

147. Dixon discloses that “[t]he time and financial burden of monthly injections [such as with ranibizumab and bevacizumab] has led to the initiation of studies to examine the efficacy of alternative dosing schedules.” *Id.* at 2.

Unfortunately, Dixon discloses that “studies seem to indicate that quarterly dosing [of ranibizumab] is associated with poorer outcomes” and that “even with the p.r.n. dosing ... patients are still required to make monthly visits to the office with frequent and expensive testing. The development of new drugs for neovascular AMD has thus focused on both improving efficacy and extending duration of action.” *Id.*

148. Dixon further discloses that “VEGF Trap-eye is a novel anti-VEGF drug currently in commercial development for the treatment of neovascular AMD by Regeneron Pharmaceuticals, Inc. .. in the US and in collaboration with Bayer HealthCare ... in global markets.” *Id.* Dixon discloses that

Structurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with human IgG Gc fragment (Figure 1). Functionally, VegF Trap-Eye acts as a receptor decoy with high affinity for all EGF isoforms, bunding more tightly than their native receptors. Unlike anti-VEGF drugs currently in use, VEGF Trap-Eye is designed to inhibit placental growth factors-1 and -2 in addition to all isoforms of VEGF-A.

Id. at 1575. Dixon discloses the following “Figure 1”

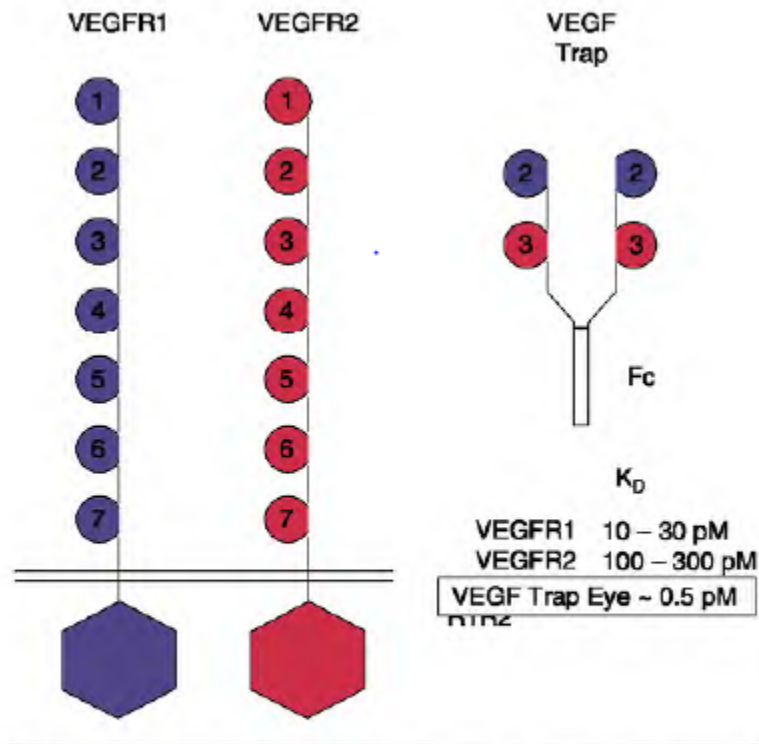


Figure 1. Schematic diagram of VEGF Trap-Eye, a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.

Id. at 1576. Dixon further explains that “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure” but that “VEGF Trap-Eye undergoes further purification steps during manufacturing to minimize risk of irritation to the eye [and] is also formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.” *Id.*

149. Dixon also discloses the clinical study history for VEGF Trap-Eye. Specifically, Dixon discloses that “[t]he safety, tolerability and biological activity of intravitreal VEGF Trap-Eye in treatment of neovascular AMD was evaluated in the

two part [CLEAR-IT-1] study in which “[n]o adverse systemic or ocular events were noted and visual acuity remained stable or improved ≥ 3 lines in 95% of patients with mean increase in BCVA of 4.6 letters at 6 weeks” while “[p]atients showed substantially decreased foveal thickness.” *Id.* “In the second part [of CLEAR-IT-1] patients “received a single intravitreal injection of either 0.5 or 4 mg ... and were followed or 8 weeks.” *Id.* “No serious adverse events or ocular inflammation was identified during the study. At 8 weeks, the mean decrease in retinal thickness in the low dose group was 63.7 μm compared to 175 μm for the high dose group.” *Id.*

150. Dixon also discloses that “VEGF Trap-Eye has also undergone a small open-label safety study for the treatment of [DME]” in which it was “administered as a single 4 mg intravitreal injection to five patients with longstanding diabetes and several previous treatments for DME. The single injection resulted in a median decrease of central macular thickness measured by OCT of 79 μm . BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks.” *Id.*

151. Dixon also discloses the “CLEAR-IT-2 trial was a prospective, randomized, multi-center, controlled dose- and interval-ranging Phase II trial” in which there were 5 dose groups: “[t]wo groups [of patients] received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of either 0.5, 2.0 or 4.0 mg for 12 weeks (at weeks 0 and

12). Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n basis.” *Id.* at 4.

152. “Patients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks. During the p.r.n. dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections and those initially dosed on a 0.5 mg monthly schedule received an average of 2.5 injections” and patients “also displayed mean decrease in retinal thickness versus baseline of 143 μm ($p < 0.0001$) in the 2.0 mg group and 125 μm ($p < 0.0001$) in the 0.5 mg group at 52 weeks as measured by OCT. Patients in the three quarterly dosing groups also showed mean improvements in BCVA and retinal thickness.” *Id.* Further, Dixon discloses that “[b]ased on Phase II study data, VEGF Trap-Eye seems to be generally well tolerated with no serious drug-related adverse events.” *Id.*

153. Dixon discloses “[a] two part Phase III trial of VEGF Trap-Eye was initiated,” VIEW 1 and VIEW 2. *Id.* “The first part, VIEW 1 ... will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye doses of 0.5 and 2.0 mg administered at 4-week dosing intervals”—i.e., doses at weeks 0, 4, 8, 12, etc.—“and 2.0 mg at an 8 week dosing interval (following three monthly doses)” —i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, 48, etc.—

“compared with 0.5 mg of ranibizumab administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n dosing evaluation.” *Id.*

154. Regarding VIEW 2, Dixon discloses that trial “has a similar study design” as VIEW 1 “and is currently enrolling patients in Europe, Asia Pacific, Japan, and Latin America.” Dixon specifically cites to NCT-377 (Ex. 1018) as a reference for its discussion of VIEW 2, which as discussed above discloses that after the first year “a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks”—i.e., doses may be administered every 4 weeks or as infrequently as every 12 weeks. *Id.* at 6. Thus, the p.r.n. dosing after the first year to which Dixon refers permits administration 12 weeks after the immediately preceding dose, including 12 weeks after the last 0.5 or 2 mg dose in year 1.

155. Dixon concludes that “[d]esireable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and decreased dosing intervals” and that “VEGF Trap-Eye represents the most promising anti-VEGF investigational drug ... [d]ue to its high binding affinity and the ability to safely inject high doses into the eye, [which may result in] longer duration of affect in the eye.” *Id.*

1. Dixon Incorporates the Information Disclosed in NCT-377 (Ex. 1018)

156. In my opinion, the information disclosed in NCT-377 is made effectively part of Dixon. As I have noted above, I understand from counsel that information disclosed in one reference may be deemed effectively part of a separate anticipatory reference, provided, the anticipatory reference identifies with particularity what specific material it incorporates and clearly indicates where that material is found.

157. In this case, Dixon's discussion of the VIEW 1 and VIEW 2 studies is supported by citations to the clinicaltrials.gov records for these trials. In particular, with respect to VIEW 2, Dixon includes a reference to endnote 47:

evaluation. The VIEW 2 [47] study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America. In both trials, the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).

Id. Endnote 47 is a citation to the clinicaltrial.gov record for NCT00637377 that was accessed on September 28, 2008:

47. VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2).
[ClinicalTrials.gov identifier: NCT00637377] ClinicalTrials.gov
[online]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00637377>
[Accessed 28 Sep 2008]

Id. at n.47. Version 4 of the clincialtrials.gov record for NCT00637377 was updated on August 4, 2008—i.e., before August 28, 2008—and version 5 was updated on

September 30, 2008—i.e., after August 28, 2008. Ex. 1018 at 2. As such, the study record that would have been accessible on September 28, 2008 and to which Dixon cites would necessarily have been version 4. And as I have already explained in Section X.M above, version 4 is the same as NCT-377 (Ex. 1018). Therefore, Dixon necessarily incorporates the information disclosed in NCT-377.

O. “Crawford” (Ex. 1026) - Talia N. Crawford, et al., *Diabetic Retinopathy and Angiogenesis*, 5 CURRENT DIABETES REVIEW, 8-13 (2009)

158. Crawford is an article that was published in the Current Diabetes Review in 2009, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Crawford qualifies as prior art.

159. Crawford discloses that “[d]iabetic retinopathy [is] a secondary microvascular complication of diabetes mellitus” and “is the leading cause of blindness in the United States amongst individuals age 20 to 64.” Ex. 1026 at 1. “Two major retinal problems cause most of the diabetes-related vision loss: [DME] and complications from abnormal retinal blood vessels growth, angiogenesis.” *Id.* Crawford further discloses that “[h]igh glucose,” a major component of diabetes, “induces hypoxia in retinal tissue, thus leading to the production of VEGF-A,” which is a powerful angiogenic inducer.” *Id.* However, due to diabetes, these

new vessels formation[s] become[] problematic because they are fragile and highly permeable” and when these “delicate vessels are disrupted easily by vitreous traction [it] leads to hemorrhage into the vitreous cavity or the

preretinal space. This stage of proliferative diabetic retinopathy (PDR) is most concerning since it poses the greatest threat of vision loss.

Id. at 2.

160. Thus by 2011, Crawford explains it was well recognized that “[s]ince VEGF-A is a powerful angiogenic inducer, utilizing anti-VEGF treatments has proved to be a successful protocol in the treatment of proliferative diabetic retinopathy.” *Id.* In fact, Crawford discloses that ranibizumab was being used by POSAs as a treatment for diabetic retinopathy. *Id.* at 4 (“Ranibizumab is administered intravitreally through injection into the pars plana.”).

P. “2009 10-Q” (Ex. 1037) - Regeneron Pharm., Inc., Quarterly Report (Form 10-Q) (Sept. 30, 2009)

161. I understand that 2009 10-Q is a legally required regulatory filing that Regeneron was required to file as a publicly traded company and which would have been published in 2009, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that 2009 10-Q qualifies as prior art.

162. 2009 10-Q discloses Regeneron’s clinical study program for aflibercept, which is also identified as “VEGF Trap.” Ex. 1037 at 18. 2009 10-Q discloses that “[a]flibercept is a protein-based product candidate designed to bind all forms of [VAGF-A], VEGF-B and the related Placental Growth Factor (PIGF), and prevent their interaction with cell surface receptors.” *Id.* 2009 10-Q teaches that “VEGF-A [and VEGFB and PIGF] [are] required for the growth of new blood

vessels (a process known as angiogenesis) that are needed for tumors to grow and is a potent regulator of vascular permeability and leakage.” *Id.*

163. 2009 10-Q discloses that “VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications” and is the subject of “a Phase 3 program in patients with the neovascular form of age-related macular degeneration (Wet AMD)” and “a Phase 2 study ... in patients with diabetic macular edema (DME).” *Id.* at 19.

164. 2009 10-Q goes on to disclose that

[t]he Phase 3 trials in wet AMD, known as VIEW 1 and VIEW 2 ... are comparing VEGF Trap-Eye and Lucentis® (ranibizumab injection).... VIEW 1 is being conducted in North America and VIEW 2 is being conducted in Europe, Asia Pacific, Japan, and Latin America. The VIEW 1 and VIEW 2 trials are both evaluating VEGF Trap-Eye doses of 0.5 milligrams (mg) and 2.0 mg at dosing intervals of four weeks and 2.0 mg at a dosing interval of eight weeks (after three monthly doses) compared with Lucentis dosed according to its U.S. label, which specifies doses of 0.5 mg administered every four weeks over the first year. As-needed dosing (PRN) with both agents will be evaluated in the second year of the studies. VIEW 1 and VIEW 2 are now fully enrolled, and initial data are expected in late 2010.

Id.

165. 2009 10-Q also discloses “a Phase 2 study [known as CLEAR-IT 2] in wet AMD which demonstrated that patients treated with VEGF Trap-Eye achieved

durable improvements in visual acuity and retinal thickness for up to one year.” *Id.*

In that trial

patients were initially treated for three months with VEGF Trap-Eye: two groups received monthly doses of 0.5 and 2.0 mg (at week 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg (at baseline and week 12). Following the initial three month fixed-dosing phase, patients continued to receive VEGF Trap-Eye at the same dose on a PRN dosing schedule through one year, based on physician assessment of the need for re-treatment in accordance with pre-specified criteria.

Id. 2009 10-Q reports that “[a]fter week 12 to week 52 in the PRN dosing period, patients initially dosed on a 2.0 mg monthly schedule received, on average, only 1.6 additional injections and those initially dosed on a 0.5 mg monthly schedule received, on average 2.5 additional injections.” *Id.*

Q. “Mitchell” (Ex. 1038) - P Mitchell et al., Ranibizumab (Lucentis) in Neovascular Age-Related Macular Degeneration: Evidence from Clinical Trials, 94 BRIT. J. OPHTHALMOLOGY 2 (2009) (date of online publication)

166. Mitchell is an article that was published in the online edition of the British Journal of Ophthalmology in 2009, which is more than one year before the earliest priority date of the ’345 patent. Ex. 1038 at 4 (“Published Online First 20 May 2009”). Therefore, I understand that Mitchell qualifies as prior art.

167. Mitchell discusses the Lucentis (ranibizumab) product for the treatment of AMD. Mitchell discloses that study “results suggest that quarterly treatment is, on average, inferior to monthly treatment and that more frequent monitoring is

needed” (*id.* at 8); “quarterly visits were insufficient to monitor and capture disease progression (*id.* at 9); and fixed monthly injections resulted in further V[isual] A[cuity] improvement during the maintenance phase.” *Id.*

R. “Heier-2009” (Ex. 1016) - Jeffery S. Heier, *VEGF Trap-Eye for Exudative AMD*, RETINAL PHYSICIAN, Apr. 2009

168. Heier-2009 was published in April 2009, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Heier-2009 qualifies as prior art.

169. Heier-2009 teaches that “[VEGF] family is a group of molecules that direct both normal and pathological processes in the body. Certain members of the family and their receptors have been implicated in the angiogenesis underlying pathological diseases processes, including development of eye diseases such as neovascular (wet) age-related macular degeneration,” which “is the leading cause of vision loss in adults aged 50 years and older.” Ex. 1016 at 1.

170. Heier-2009 discloses that “Regeneron’s VEGF Trap-Eye has been developed exclusively for ophthalmic use. The ophthalmic formulation is specifically purified and formulated as an iso-osmotic solution to avoid irritation of the eye.” Heier-2009 further discloses that “[b]ased on its unique binding properties (which are distinct from VEGF antibodies/antibody fragments), predictive modeling studies indicate that VEGF Trap-Eye should have a longer duration of activity than currently available treatments.” *Id.* at 3.

171. Heier-2009 teaches the mechanism of action for VEGF Trap-Eye:

Each arm of VEGF Trap-Eye binds to the binding interface on each pole of the active VEGF or PlGF dimer. This forms a stable and inert 1:1 complex with the growth factor, uniquely binding the dimer on both sides. The Trap is aptly named, since the molecule isolated (or traps) the dimer, forming inert complexes with the growth factor that do not interact with more than 1 VEGF angiogenesis cascade. It also prevents the creation of multimeric complexes that might aggregate and cause immune responses in body tissues.

Id.

172. Heier-2009 discloses the two part phase I CLEAR-IT-1 study. In part 1 “a single, ascending-dose 6-week study. One intravitreal VEGF Trap-Eye injection was given (0.05, 0.15, 0.5, 1, 2, or 4 mg), which reduced retinal thickness and improved visual acuity for the combined experimental groups vs baseline. BCVA scores improved by a mean of 4.4 letters and central retinal lesion thickness diminished by 78.8 μ m. The effects of VEGF Trap-Eye appeared durable; patients averaged >5 months before retreatment was necessary in an extension study, with a mean time to retreatment of 166 days.” *Id.* at 2. In Part 2 of the study patients were administered intravitreal VEGF Trap-Eye injection of 0.15 or 4 mg. *Id.*

Both doses diminished retinal thickness at 2 weeks, with a significantly greater reduction in retinal thickness in the 4-mg group at weeks 4 and 8. The 4-mg dose significantly improved visual acuity at 4, 6, and 8 weeks. In both parts of this study, intravitreal injection of up to 4 mg of VEGF Trap-Eye was well tolerated, with no clinically significant intraocular inflammation.

Id.

173. Heier also discloses the Phase 2 CLEAR-IT 2 study. in which “Patients were randomized into 5 groups (N=159 randomized, N=157 treated) and treated with VEGF Trap-Eye in the study eye at 0.5 mg and 2.0 mg q4 weeks, and 0.5, 2.0, and 4.0 mg q12 weeks for 12 weeks, followed by as-needed (prn) dosing through week 52.” *Id.* “During the prn dosing period from week 12 to week 52, patients from all dose groups combined received, on average, only 2 additional injections.” *Id.* Heier further reports that “prn dosing following a fixed quarterly dosing regimen (with dosing at baseline and week 12) also yielded improvements in visual acuity and retinal thickness vs baseline at week 52.” *Id.*

174. Heier goes on to disclose the Phase 3 VIEW 1 and VIEW 2 studies in which “[f]our treatment groups will be followed for 52 weeks: 3 VEGF Trap-Eye treatment groups, 0.5 mg q 4 weeks, 2.0 mg q 4 weeks, and 2.0 mg q 8 weeks will be compared with ranibizumab 0.5 mg q 4 weeks.” *Id.*

S. “Nguyen-2009” (Ex. 1006) - Quan Dong Nguyen et al., A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration, 116 OPHTHALMOLOGY 2141 (2009)

175. Nguyen is an article published in 2009, which is more than one year before the earliest priority date of the '345 patent. Therefore, I understand that Nguyen-2009 qualifies as prior art.

176. Nguyen discloses that in a Phase I study (CLEAR-IT 1) “[i]ntravitreal injection of up to 4 mg of VEGF Trap-Eye in patients with [neovascular AMD] was well tolerated with no evidence of ocular inflammation” and that “there was no evidence of bioactivity, because several patients, especially those receiving 2 or 4 mg of VEGF Trap-Eye, showed substantial improvement in BCVA associated with reduction in foveal thickness.” Ex. 1006 at 1.

T. “Adis” (Ex. 1008) – Adis R&D Profile, Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye, 9 DRUGS R&D 261 (2008)

177. Adis is an article published in Adis’s Drugs in R&D journal in 2008, which is more than one year before the earliest priority date of the ’345 patent. Therefore, I understand that Adis qualifies as prior art.

178. Adis discloses information about “aflibercept”, which it also identifies as “VEGF Trap (R1R2)” and “VEGF Trap-Eye.” Ex. 1008 at 1. Adis discloses that “Aflibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and third Ig domain of VEGFR2, fused to the Fc region of human IgG” and that “Regeneron and Bayer are developing the agent for eye disorders.” *Id.* Adis further discloses that “Aflibercept binds to all VEGF-A isoforms as well as placental growth factor (PIGF), thereby preventing these factors from stimulating angiogenesis. Blockage of VEGF can also prevent blood vessel formation and vascular leakage associated with [AMD].” *Id.*

179. Adis also discloses that “Regeneron and Bayer initiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007” called “VIEW 1” that “will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals, and 2.0 mg at 8-week dosing interval, compared with 0.5 mg ranibizumab administered every 4 weeks.” *Id.* at 3. Adis goes on to also disclose that “A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008” that “will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at 8-week dosing interval, including one additional 2.0 mg dose at week 4” and “[t]he primary endpoint will be the proportion of patients treated with aflibercept who maintain vision at the end of 1 year compared with ranibizumab patients.” *Id.*

180. Adis also summarizes prior clinical studies involving Ranibizumab. For example, it discloses that “[r]esults from an earlier phase I trial assessing the safety and tolerability of intravenous infusions of aflibercept in patients with wet AMD have ... show[n] that the efficacy endpoint was met.” *Id.* at 4. Adis also discloses “a phase I trial of aflibercept in five patients with [DME] ... indicated that a single 4 mg injection resulted in a marked decrease in mean central retinal thickness and mean macular volume throughout the 6-week observation period” and

that aflibercept “was generally well tolerated, and there were no drug-related serious adverse events.” *Id.* at 3.

181. Adis also discloses that “Regeneron has completed a 12-week, phase II Trial in patients with wet AMD” in which “[t]wo patient groups received monthly doses of 0.5 and 2.0 mg, and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg (baseline and week 12).” *Id.* “Analysis of data demonstrated that all five doses of aflibercept met the primary study endpoint of a statistically significant reduction in retinal thickness after 12 weeks and 32 weeks of treatment compared with baseline.” *Id.* Adis further discloses that “[f]ifty-five percent of patients receiving 2.0 mg monthly for 12 weeks did not require any additional treatment throughout the next 20 week PRN dosing period.” *Id.* at 8.

182. Adis discloses a comprehensive “Drug development history” for aflibercept starting from May 2000 through May 2008. *Id.* at 5-7.

183. A review of the citations at the end of Adis, show that the majority of the information about aflibercept, including regarding the Phase 2 and Phase III studies reported in Adis were derived from Regeneron and Bayer press releases—some of which are the same press releases that I discuss in this declaration.

- U. **“Regeneron (2008-May-08)” (Ex. 1022) – Regeneron. [Press Release] Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age Related Macular Degeneration (2008, May 8).**

184. Regeneron (2008-May-08) is a press release published by Regeneron on May 8, 2008, which is more than one year before the earliest priority date of the '345 patent. Therefore, I understand that Regeneron (2008-May-08) qualifies as prior art.

185. Regeneron (2008-May-08) announced to the public that “the first patient has been dosed in the VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of the neovascular form of ... wet AMD, a leading cause of blindness in adults.” Regeneron (2008-May-08) at 1.

186. Regeneron (2008-May-08) discloses the following quote from “Kemal Malik, MD, Head of Global Development and member of the Bayer HealthCare Executive Committee”: “Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision.” *Id.* It also discloses the following quote from “George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories” and the named inventor for the '345 patent: “New therapies are still needed to provide optimal care to those patients with wet AMD. This global Phase 3 clinical program will provide additional data to further evaluate the efficacy and safety of VEGF Trap-Eye using different dosing regimens.” *Id.*

187. Regeneron (2008-May-08) discloses that “[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 week.” *Id.* Regeneron (2008-May-08) further discloses that

[i]n the first year, the VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every 4 weeks. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but not more often than every 4 weeks until the end of the study.

Id.

188. Regarding the Phase 2 study, Regeneron (2008-May-08) discloses that “VEGF Trap-Eye met both primary and secondary key endpoints” and that

[f]ollowing the initial 12-week fixed-dosing phase of the trial, patients continued to receive therapy at the same dose on a PRN (as needed) dosing schedule based upon the physician assessment of the need for re-treatment in accordance with prespecified criteria. At the 2008 meeting of the Association for Vision and Ophthalmology (ARVO), it was reported that, on average, patients on the PRN dosing schedule maintained the gain in visual acuity and decrease in retinal thickness achieved at week 12 through week 32 of the study.

V. “The ’758 patent” (Ex. 1012) – U.S. Patent No. 7,374,758

189. The '758 patent was issued on May 20, 2008, which is more than one year before the earliest priority date for the '345 patent. Therefore, I understand that the '758 patent qualifies as prior art.

190. The '758 patent is titled “Modified Chimeric Polypeptides with Improved Pharmacokinetic Properties and Methods of Using Thereof.” On its face, the '758 patent is assigned to Regeneron and names three inventors, including George D. Yancopoulos, who is also the named inventor for the '345 patent. Ex. 1012 at (73), (75).

191. The '758 patent discloses that “the method of the invention may be useful in treating clinical conditions that are characterized by vascular permeability” including “eye disorders such as age related macular degeneration and diabetic retinopathy.” *Id.* at 15:50-16:6.

192. The '758 patent further discloses the VEGF fusion polypeptide (i.e., VEG Trap-Eye/aflibercept) disclosed as preferred embodiments in the '173 patent discussed below. Specifically, the '758 patent discloses in Figure 24A-C the annotated sequence of VEGFR1R2-Fc Δ C1(a), which includes the signa; sequence (aa 1-26); the Flt-1 Ig domain 2 (aa 27-129); the Flk-1 Ig domain 3 (aa 130-231); and the Fc domain (aa 232-458). *Id.*, Fig. 24A-C; *see also id.* at 10:15-17 (“Nucleotide (SEQ ID NO:15) and deduced amino acid sequence (SEQ ID NO:16) of the modified Flt1 receptor termed VEGFR1R2-Fc Δ C1(a).”).

W. “The ’173 patent” (Ex. 1010) – U.S. Patent No. 7,531,173

193. The ’173 patent was issued on May 12, 2009, which is more than one year before the earliest priority date for the ’345 patent. Therefore, I understand that the ’173 patent qualifies as prior art.

194. The ’173 patent is titled “Ophthalmic Composition of VEGF Antagonist.” On its face, the ’173 patent is assigned to Regeneron. ’173 patent at (73).

195. The ’173 patent discloses “agents capable of blocking, inhibiting or ameliorating VEGF-mediated activity is a VEGF antagonist” that includes the “VEGFR1R2-Fc Δ C1(a) (also termed VEGF trap_{R1R2}) comprising the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2.” *Id.* at 1:42-53.

196. The nucleotide and amino acid sequences for VEGF antagonist fusion protein disclosed in the ’173 patent are identical to the VEGF antagonist sequence required by the Challenged Claims of the ’345 patent. (*Compare* Ex. 1001, SEQ ID NO:1 and SEQ ID NO:2 *with* Ex. 1010 at 1:42-56, SEQ ID NOS: 1 and 2).

X. “Massin” (Ex. 1044) – Pascale Massin, et al., *Safety and Efficacy of Ranibuzimab in Diabetic Macular Edema (RESOLVE Study)*. DIABATES CARE, Volume 33, Number 11 (November 2010).

197. Massin was published in November 2010, which is before the earliest priority date of the '345 patent. Therefore, I understand that Massin qualifies as prior art.

198. Massin discloses that “VEGF promotes neovascularization and microvascular leakage. Thus, inhibiting VEGF may provide an alternative therapeutic approach in [DME]”. Ex. 1043 at 1. Massin further discloses that “[r]anibizumab is a fully humanized monoclonal antibody fragment (Fab), which binds to multiple variants of VEGF-A, and is approved for the treatment of nAMD.” *Id.* at 1-2.

199. Massin further discloses “the results of the phase II RESOLVE study in patients with VI due to DME” *Id.* at 2. Massin reports that “[r]anibizumab led to significant and continuous improvement in both BCVA and CRT over 12 months compared with sham treatment in patients with VI due to DME.” *Id.* at 5. Massin further reports that “[r]esults from the RESOLVE study indicate that DME responds well to treatment with intravitreal ranibizumab over 1 year.” *Id.* at 6.

Y. “Regeneron (18-Feb-2010)” (Ex. 1052) – Regeneron. [Press Release] VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients with Diabetic Macular Edema (Feb. 18, 2010)

200. Regeneron (18-Feb-2010) is a Regeneron press release that was published February 18, 2010, which is more than one year before the earliest priority

date of the '345 patent. Therefore, I understand that Regeneron (18-Feb-2010) qualifies as prior art.

201. Regeneron (18-Feb-2010) discloses “that VEGF Trap-Eye showed positive results in a Phase 2 study in patients with [DME]. The primary endpoint of the study, a statistically significant improvement in visual acuity over 24 weeks compared to the standard of care in DME, macular laser therapy, was met. Visual acuity improvement was measured by the mean number of letters gained over the initial 24 weeks of the study.” Ex. 1022 at 1.

202. Regeneron (18-Feb-2010) discloses a quote from “Dr. Kemal Malik, member of the Bayer HealthCare Executive Committee’ in which he says “The ability of VEGF Trap-Eye to significantly improve vision in patients with DME in this initial Phase 2 study is encouraging,” and that “Bayer and Regeneron will discuss the next steps in further developing VEGF Trap-Eye in this indication.” *Id.*

203. Regeneron (18-Feb-2010) also discloses a quote from “Diana Do, MD, the Principal Investigator for the study and Assistant Professor Ophthalmology at the Wilmer Eye Institute, The John Hopkins University School of Medicine in Baltimore, Maryland” in which she states “The magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this Phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high level of vascular endothelial growth factor (VEGF) are present.” *Id.*

XI. UNPATENTABILITY OF THE '345 PATENT

204. I was asked to review the '345 patent and provide an opinion as to whether the Challenged Claims are invalid in view of the prior art. For reasons set forth in the following sections, it is my opinion that the Challenged Claims of the '345 patent are anticipated by any one of Dixon, NCT-795, and Regeneron (8-May-2008). It is also my opinion that the Challenged Claims of the '345 patent are obvious over Dixon and any one of NCT-795, NCT-377, and Regeneron (8-May-2008).

A. DIXON (Ex. 1007) AND NCT-377 (Ex. 1018) INVALIDATE THE CHALLENGED CLAIMS

205. In my discussion of Dixon above (See Section X.N.1), I explain that Dixon necessarily incorporates NCT-377 and the information disclosed therein. Thus, in coming to my opinion that Dixon anticipates the Challenged Claims, I rely on the disclosures in both Dixon and NCT-377. However, even if the Board determines that Dixon does not incorporate the information disclosed in NCT-377, as I show below, NCT-377 itself also anticipates the Challenged Claims. And alternatively, the Challenged Claims are obvious over Dixon in view of NCT-377.

1. Claim 1 is Anticipated by Dixon and/or NCT-377, and Obvious over Dixon In View of NCT-377 and a POSA's knowledge

a) "A method for treating an angiogenic eye disorder in a patient, said method"

206. Dixon discloses “[a] two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007.” Ex. 1007 at 4. Specifically, it discloses that the first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) will enroll ~ 1200 patients with neovascular AMD in the US and Canada” and that the second part “VIEW 2 study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America.” *Id.*

207. Additionally, NCT-377, which is incorporated into Dixon (*see* Section X.N.1 above), also discloses that the VIEW 2 study is “A Randomized, Double Masked, Active Controlled, Phase 3 Study of Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related Macular Degeneration (AMD).” Ex. 1018 at 5.

208. As of 2011, a POSA would have known that “wet age-related macular degeneration” is a type of angiogenic eye disorder. Moreover, a POSA would have understood that a study involving administration of a drug for the treatment of wet AMD would require a methods of treatment.

209. Therefore, Dixon and/or in view of NCT-377 discloses “a method for treating an angiogenic eye disorder in a patient.”

- b) **“comprising sequentially administering to the patient a single initial dose of VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of VEGF antagonist”**

210. Dixon discloses that the VIEW 1 and VIEW 2 studies “will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals” and that “[a]fter the first year of the study, patients will enter a second year of p.r.n. dosing evaluation.” Ex. 1007 at 4.

211. Additionally, NCT-377, which is incorporated into Dixon (*see* Section X.N.1 above), also discloses the following dosing regimen to be used in VIEW 2:

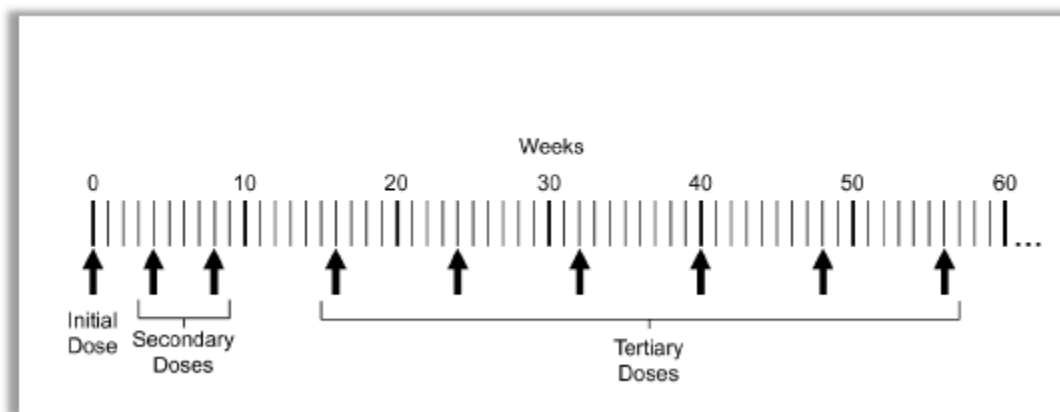
- “0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” (Ex. 1018 at 8-9)
- “2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” (Ex. 1018 at 9)

Thus, a POSA would understand that Dixon learned of the VIEW 2 dosing regimen from NCT-377. More specifically, a POSA would understand that Dixon’s reference to “p.r.n dosing” “after the first year” refers to “dose[s] [that] may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.”

212. Furthermore, a POSA reviewing the specification for the ’345 patent including Figure 1 would understand that (i) the first 0.5 mg or 2.0 mg VEGF Trap-Eye/aflibercept administration in the VIEW 2 study *as disclosed in Dixon* and NCT-377 would be the claimed “single initial dose” of VEGF Trap-Eye/aflibercept; and

(ii) the doses after the single initial dose that are administered “every 4 weeks during the first year” of VIEW 2 study would be “one or more secondary doses.” The specification for the ’345 patent supports this conclusion.

213. The ’345 patent states that FIG. 1 “shows an exemplary dosing regimen of the present invention.” Ex. 1001 at 2:63-64. I provide FIG. 1 from the ’345 patent below for reference:



The ’345 patent further explains that “[i]n this regimen, a single ‘initial dose’ of VEGF antagonist ... is administered at the beginning of the treatment regimen (i.e., at week 0), two ‘secondary doses’ are administered at weeks 4 and 8, respectively.” *Id.* at 2:64-67. Similarly, in the VIEW 2 study as disclosed in Dixon and NCT-377, the first dose, which would necessarily have to be at 0 weeks—i.e., at the very start of the study—is the “initial dose.” The dose immediately following the dose at 0 weeks would therefore then be the start of any “secondary doses.” And in the case of the VIEW 2 study as disclosed in Dixon and NCT-377, the doses administered

“every four weeks during the first year” after the first initial dose at week 0 would be the claimed “one or more secondary doses.”

214. Finally, a POSA would understand that doses administered after the first year would be the claimed tertiary dose as these doses do not necessarily have to be every 4 weeks since Dixon discloses that these doses are administered “p.r.n.” or as -needed, which NCT-377 further discloses means “no less frequent[] than every 12 week.”

215. Therefore, Dixon alone and/or in view of NCT-377 discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist.

c) “wherein each secondary dose is administered 4 weeks after the immediately preceding dose”

216. Dixon discloses that VIEW 1 and VIEW 2 dosing regimen includes “intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing interval.” Ex. 1007 at 4. Further, as I have explained above, Dixon incorporates the information disclosed in NCT-377. As I have also explained above, a POSA would understand that, pursuant to the “Assigned Interventions” disclosed in NCT-377, the doses after the single initial dose that are administered—i.e., “every

4 weeks during the first year”—would be “one or more secondary doses,” and these doses would be administered after the immediately preceding initial dose.

217. Therefore, Dixon alone and/or in view of NCT-377 discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

d) “wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.”

218. As I have explained above, Dixon incorporates the information disclosed in NCT-377. As I have also explained above, a POSA would understand that Dixons’ disclosure of “p.r.n.” dosing “after the first year” refers to “dose[s] [that] may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” pursuant to the “Assigned Interventions” disclosed in NCT-377”—meaning they can, in fact, be as infrequent as every 12 weeks, including 12 weeks after the final 0.5 or 2.0 mg “secondary dose” at the end of the first year.

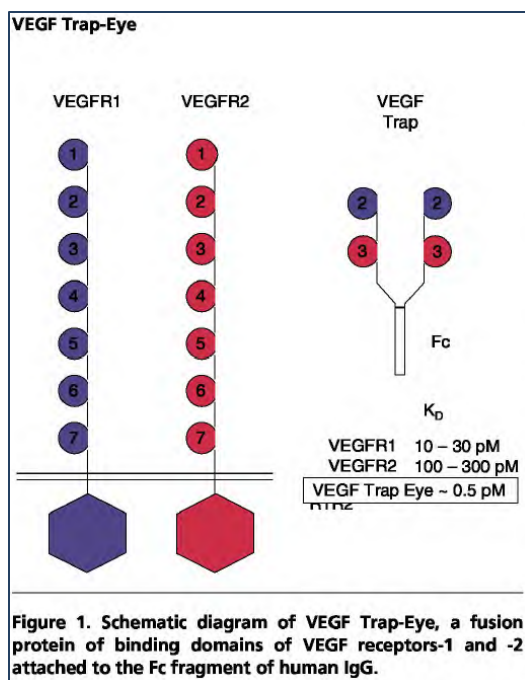
219. Therefore, Dixon alone and/or in view of NCT-377 discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one

or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.

- e) **“wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1 and a multimerizing component.”**

220. A POSA would understand this limitation is merely a recitation of the domain composition of aflibercept/VEGF Trap-Eye disclosed in Dixon and NCT-377. This was well known long before 2011. As such the VEGF Trap-Eye disclosed in Dixon and NCT-377 inherently meet this limitation.

221. Dixon disclosed that “[s]tructurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment” and provides the below Figure:



Ex. 1007 at 3; Fig. 1.; Ex. 1005 at 1-2 (disclosing “VEGF-Trap_{R1R2} was created by fusing a second Ig domain of VEGFR1 with the third Ig domain of VEGFR2.”); Ex. 1032 at 413 (disclosing “a chimeric fusion protein containing a modified domain 2 of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc region of human IgG1, resulting in a fully human protein that we term VEGF Trap.”); Ex. 1033 at 2 (disclosing that “VEGF Trap is a recombinant soluble VEGF receptor protein in which the binding domains of VEGF receptors 1 and 2 are combined with the Fc portion of immunoglobulin G.”); Ex. 1034 at 1 (disclosing that “VEGF Trap is a fully human soluble decoy receptor protein that consists of a fusion of the second Ig domain of human VEGF receptor (VEGFR) 1 and the third Ig domain of human VEGFR2 with the constant region (Fc) of human Ig IgG1.”); Ex. 1035 at 4 (disclosing “VEGF Trap is a soluble chimeric receptor in which key domains of

VEGFR1 (domain 2) and VEGFR2 (domain 3) are fused to the constant region (Fc portion) of human IgG1 [34]. This fully human protein is capable of binding all isoforms of VEGF-A with very high affinity (KD <0.5 pM for hVEGF165). Moreover, and in contrast to antibodies directed against VEGF-A, the VEGF Trap also binds PlGF, a VEGF family member also implicated in pathological angiogenesis [46] (KD ~25 pM for hPlGF2)”).; Ex. 1037 at 18 (Regeneron disclosing its clinical study program for aflibercept which it identifies as “VEGF Trap.”); Ex. 1012 at Fig. 234A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain)), 10:15-17 (specifying that this molecule is termed “VEGFR1R2-FcΔC1(a).”); Ex. 1008 at 1 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug.”).

222. Therefore, Dixon alone and/or in view of NCT-377 discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each

tertiary dose is administered 12 weeks after the immediately preceding dose; wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.

2. Claim 2 is Anticipated by Dixon and/or NCT-377, and Obvious over Dixon In View of NCT-377 and a POSA's knowledge

223. Claim 2 of the '345 patent depends from claim 1. Therefore, I incorporate my opinions with respect to claim 1 herein. Claim 2 further requires “wherein the VEGF antagonist is aflibercept.”

224. As discussed above with respect to claim 1, VEGF Trap-Eye which is the compound used in the method of treating AMD that is disclosed in Dixon and NCT-377 is necessarily aflibercept. In fact, in its 2009 10-Q filing, Regeneron identifies aflibercept as being the same as “VEGF Trap” (Ex. 1037 at 17 (“Our late stage programs are aflibercept (VEGF Trap)”); that “VEGF Trap-Eye is a specifically purified and formulated form of VEGF Trap for use in intraocular applications” (*id.* at 19); and that VEGF Trap-Eye is undergoing “Phase 3 trials in wet AMD, known as VIEW 1 and VIEW 2.” *Id.* See also, Ex. 1008 at 1 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a POSA to refer, interchangeably, to the same drug.”).

225. Therefore, Dixon alone and/or in view of NCT-377 discloses the method of claim 1, wherein the VEGF antagonist is aflibercept.

3. Claims 3-4 Are Anticipated by Dixon and/or NCT-377, and Obvious over Dixon In View of NCT-377 and a POSA's knowledge

226. Claims 3 and 4 ultimately depend from claim 1. Therefore, I incorporate my opinions with respect to claim 1 herein. Claims 3 and 4 further requires “wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration” (claim 3) and “wherein the intraocular administration is intravitreal administration” (claim 4).

227. Dixon discloses that the VIEW 1 and VIEW 2 studies are “non-inferiority stud[ies] [that] will evaluate the safety and efficacy of *intravitreal* VEGF Trap-Eye at doses of 0.5 and 2.0 mg.” Ex. 1007 at 4 (emphasis added).

228. Further, as I explained above, Dixon incorporates the information disclosed in NCT-377. NCT-377 discloses Phase III study with an “Official Title”: “A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of *Intravitreal VEGF Trap* in Subjects With Neovascular Age-Related Macular Degeneration.” Ex. 1018 at 5 (emphasis added).

229. Therefore, Dixon alone and/or in view of NCT-377 discloses the method of claim 1, wherein all doses of the VEGF antagonist are administered to the

patient by intraocular administration (claim 3) and wherein the intraocular administration is intravitreal administration (Claim 4).

4. Claims 5-7 Are Anticipated by Dixon and/or NCT-377, and Obvious over Dixon In View of NCT-377 and a POSA's knowledge

230. Claims 5-7 depend from claim 4. Therefore, I incorporate my opinions with respect to claim 4 herein. Claims 5, 6, and 7 also requires “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist” (claim 5); “wherein all doses ... comprise 0.5 mg of the VEGF antagonist” (claim 6); and “wherein all doses ... comprise 2 mg of the VEGF antagonist (claim 7).

231. As discussed above with respect to claim 1, Dixon discloses that the VIEW 1 and 2 studies “will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at *doses of 0.5 and 2.0 mg.*” Ex. 1007 at 4 (emphasis added).

232. Also, as I have discussed above, Dixon incorporates the information disclosed in NCT-377. Regarding VIEW 2, NCT-377 discloses several study groups including a 0.5 mg dose and a 2.0 mg dose “administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.” Ex. 1018 at 8, 9.

233. Therefore, Dixon alone and/or in view of NCT-377 discloses the method of claim 4, “wherein all doses of the VEGF antagonist comprise from about

0.5 mg to about 2 mg of the VEGF antagonist” (claim 5); “wherein all doses ... comprise 0.5 mg of the VEGF antagonist” (claim 6); and “wherein all doses ... comprise 2 mg of the VEGF antagonist (claim 7).

5. Claims 8 and 9 Are Anticipated by Dixon and/or NCT-377, and Obvious over Dixon In View of NCT-377 and a POSA’s knowledge

234. Claims 8 and 9 depend from claim 5. Therefore, I incorporate my opinions with respect to claim 5 herein. Claims 8 and 9 also require “wherein the angiogenic eye disorder is selected from the group, consisting of: age related macular degeneration, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization” (claim 8); and “wherein the angiogenic eye disorder is age related macular degeneration” (claim 9).

235. As discussed above with respect to claim 1, Dixon discloses that the VIEW 1 and VIEW 2 studies will be administered to treat patients with “Wet age-related macular degeneration.” Ex. 1007 at 4.

236. Also, as discussed above, Dixon incorporates the information disclosed in NCT-377. NCT-377 discloses a method of administering VEGF Trap-Eye for the treatment of “wet age-related macular degeneration (AMD).” Ex. 1018 at 1.

237. Therefore, Dixon alone and/or in view of NCT-377 discloses the method of claim 5, “wherein the angiogenic eye disorder is selected from the group, consisting of: age related macular degeneration, diabetic macular edema, central

retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization” (claim 8); and “wherein the angiogenic eye disorder is age related macular degeneration” (claim 9).

6. Claims 10 and 11 are Obvious Over Dixon (including NCT-377) in View Regeneron (18-Feb-2010) and a POSA’s Knowledge

238. Claims 10 and 11 depend from claim 8. Therefore, I incorporate by opinions with respect to Claim 8 herein. Claims 10 and 11 also require “wherein the angiogenic eye disorder is diabetic retinopathy” (claim 10) and “wherein the angiogenic eye disorder is diabetic macular edema (claim 11).

239. In my opinion, a POSA as of 2011 would have been motivated with a reasonable expectation of success to apply the dosing regimen disclosed in Dixon (and NCT-377, which is incorporated therein) to the treatment of diabetic macular edema (and therefore also diabetic retinopathy) in view of the positive Phase II study data disclosed in Regeneron (18-Feb-2010), and a POSA’s knowledge that (i) VEGF plays a major role in the pathogenesis of vasogenic eye disorders, including AMD, diabetic retinopathy and diabetic macular edema; (ii) VEGF antagonists had been shown to be effective in the treatment of vasogenic eye disorders; and (iii) VEGF Trap-Eye/aflibercept was a known VEGF-antagonist that had been shown to be effective in treating diabetic retinopathy with less frequent administration.

240. In 2010, Regeneron disclosed results from a Phase 2 study of VEGF Trap-Eye in patients with DME that would have motivated a POSA to treat DME using the claimed dosing regimen, which had already been disclosed in each of Dixon, NCT-377, NCT-795, and Regeneron (8-May-2008). Ex. 1052. Specifically, Regeneron reported:

that VEGF Trap-Eye showed *positive results* in a Phase 2 study in patients with diabetic macular edema (DME). The primary endpoint of the study, a statistically significant improvement in visual acuity over 24 weeks compared to the standard of care in DME, macular laser therapy, was met. Visual acuity improvement was measured by the mean number of letters gained over the initial 24 weeks of the study.

Ex. 1052 at 1 (emphasis added). Regeneron (8-Feb-2010) at 1.

241. Regeneron (18-Feb-2010) further summarized the mean gain in visual acuity at week 24 dosing arm and the mean number of treatments received by patients over the first six monthly visits:

- VEGF Trap Eye 0.5 mg monthly (n=44; 5.6 injections): +8.6 letters gained
- VEGF Trap-Eye 2 mg monthly (n=44; 5.5 injections): +11.4 letters gained
- VEGF Trap-Eye 2 mg every other month, following 3 monthly injections (n=42: 3.8 injections): +8.5 letters gained

- VEGF Trap-Eye 2 mg as-needed, following 3 monthly injections (n=45; 4.4 injections): +10.3 letters gained

Id. All of the above reported data would collectively have motivated a POSA to administer VEGF Trap-Eye according to the claimed dosing regimen. And in fact, POSAs in the field recognized these results would motivate further application of VEGF Trap-Eye for the treatment of DME and provided a reasonable expectation of success. For example, “Dr. Kemal Malik, member of the Bayer HealthCare Executive Committee” asserted that “[t]he ability of VEGF Trap-Eye to significantly improve vision in patients with DME in this initial Phase 2 study is encouraging,” and that “Bayer and Regeneron will discuss the next steps in further developing VEGF Trap-Eye in this indication.” *Id.* “Diana Do, MD, the Principal Investigator for the study and Assistant Professor Ophthalmology at the Wilmer Eye Institute, The John Hopkins University School of Medicine in Baltimore, Maryland” asserted that “[t]he magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this Phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high level of vascular endothelial growth factor (VEGF) are present.” *Id.* Thus, based on the disclosures of Regeneron (18-Feb-2010) alone, a POSA would have been motivated to administer VEGF Trap-Eye/aflibercept according to the claimed dosing regimen for the treatment of DME and therefore also diabetic retinopathy.

242. The phase 2 data for “VEGF Trap-Eye 2 mg *as needed*” for which there was “+10.3 letters gained” would have especially motivated a POSA to administer VEGF Trap-Eye/aflibercept according to the claimed dosing regimen because it showed that patients would not necessarily require monthly dosing for an extended period of time to gain an improvement in visual acuity. A POSA would have rather understood that for at least some patients less frequent administration would be sufficient after a term of fixed monthly dosing. Further, in view of Dixon’s and NCT-377’s disclosure that VEGF would be administered according to the claimed dosing regimen, it would have been obvious to also at least try to use that same dosing regimen for the treatment of DME.

243. A POSA would also have been motivated with a reasonable expectations of success to apply the VIEW 1 & 2 dosing regimen disclosed in Dixon and NCT-377 based on a POSA’s knowledge regarding the common pathogenesis of AMD and diabetic retinopathy and that VEGF Trap-Eye had been reported to be effective in treating angiogenic eye disorders with less frequent administration compared to other VEGF-antagonists.

244. As of 2011, POSAs understood that macular eye diseases, including specifically AMD, diabetic retinopathy and DME share a common pathogenesis in that upregulation of VEGF leads to harmful angiogenesis in the eye. The

“Background” section of the ’345 patent summarizes what was known to POSAs as of the priority date of the Challenged Claims:

Several eye disorders are associated with pathological angiogenesis. For example, the development of [AMD] is associated with a process called choroidal neovascularization (CNV). Leakage from the CNV causes macular edema and collection of fluid beneath the macula resulting in vision loss. ***Diabetic macular edema (DME) is another eye disorder with an angiogenic component.*** Clinically significant DME occurs when fluid leaks into the center of the macula, ...[which] can cause severe vision loss or blindness. [VEGF] contributes to increased vascular permeability in the eye and inappropriate new vessel growth.

Ex. 1001 at 1:31-54 (emphasis added). *See, also*, Ex. 1032 at 4 (“a variety of studies have indicated that VEGF may play a key pathological role in vascular eye diseases, in particular in [DME] and retinopathy settings, and in [AMD]. In these diseases, excess VEGF is thought to result in vascular leak that contributes to abnormal swelling of the retina and resulting vision impairment, as well as in the abnormal growth of choroidal and retinal vessels that can destroy normal retinal architecture.”); Ex. 1024 at 2 (“[p]erhaps more promising as the angiogenic factor of diabetic retinopathy is the family of [VEGF]”); *id.* ([i]n the context of diabetic retinopathy, [VEGF] [is] upregulated by hypoxia” and “VEGF has been reported to be present in increased amounts in the aqueous and vitreous patients with all grades of diabetic retinopathy, particularly those with proliferative disease.”); Ex. 1026 at 1 (“[h]igh glucose induces hypoxia in retinal tissue, thus leading to the production of VEGF-

A,” which is “a powerful angiogenic inducer.”); *id.* at 9 (These “new vessels formation[s] become[] problematic because they are fragile and highly permeable” and when these “delicate vessels are disrupted easily by vitreous traction [it] leads to hemorrhage into the vitreous cavity or the preretinal space. This stage of proliferative diabetic retinopathy (PDR) is most concerning since it poses the greatest threat of vision loss.”); Ex. 1012 at 3:5-8 (“Persistent angiogenesis may cause or exacerbate certain diseases such as ... diabetic retinopathy.”); Ex. 1007 at 2 (“The pathogenesis of C[horoidal] N[eo]vascularization] in the setting of AMD is complex; however, there is overwhelming evidence that VEGF is a prominent mediator in its genesis.”); Ex. 1043 at [0003], [0074] (“[a]ngiogenesis is implicated in the pathogenesis of intraocular neovascular diseases” including, “e.g., ... [AND], diabetic and other ischemia-related retinopathies, diabetic macular edema, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, Central Retinal Vein Occlusion (CRVO), corneal neovascularization, retinal neovascularization, etc.”).

245. As such, as of 2011, POSAs knew that anti-VEGF antagonists would be useful in the treatment regimen for patients with AMD, diabetic retinopathy, and DME. *See, e.g.,* Ex. 1026 at 1 (“Since VEGF-A is a powerful angiogenic induce, utilizing anti-VEGF treatments has proved to be a successful protocol in the treatment of proliferative diabetic retinopathy”); Ex. 1012 at 3:8-13 (“An inhibitor

of VEGF activity would be useful as a treatment for [diabetic retinopathy] and vascular permeability conditions, such as tumor vascularization.”); Ex. 1007 at 1 (“agents that inhibit VEGF has largely supplanted ... previous treatments” for subfoveal choroidal neovascularization, including AMD.”); *id.* at 1574 (“Higher levels of VEGF expression have been demonstrated in animal models and human studies of eyes with AMD, and antagonism of VEGF in both settings have definitively demonstrated inhibition of neovascularization and vascular permeability.”). The ’345 patent background section also explains that “FDA-approved treatments of angiogenic eye disorders such as AMD and CRVO include the administration of an anti-VEGF antibody called ranibuzimab (Lucentis® Genentech, Inc.) on a monthly basis by intravitreal injection” and that “[m]ethods for treating eye disorders using VEGF antagonists are mentioned in, e.g., U.S. Pat. Nos. 7,303,746; 7,306,799; 7,300,563; 7,303,748; and US 2007/0190058.” Ex. 1001 at 1:57-60.

246. Indeed, as of 2011, VEGF-antagonists had been shown to be effective in treating angiogenic eye disorders with less frequent administration over time. *See, e.g.,* Ex. 1007

247. at claim 21 (“[a] method for treating intraocular neovascular disease, comprising: administering to a mammal a number of first individual doses of an VEGF antagonist; followed by administering to the mammal a number of second

individual doses of the antagonist, wherein the second individual doses are administered less frequently than the first individual doses.”); Ex. 1007 at 2 (“antagonism of VEGF in [animal studies and human studies of eyes with AMD] have definitively demonstrated inhibition of neovascularization and vascular permeability.”); Ex. 1012 at 15:50-16:6 (the method of the invention may be useful in treating clinical conditions that are characterized by vascular permeability” including “eye disorders such as age related macular degeneration and diabetic retinopathy.”); Ex. 1044 at 5 (“[r]anibizumab led to significant and continuous improvement in both BCVA and CRT over 12 months compared with sham treatment in patients with VI due to DME.”).

248. However, as of 2011, POSAs were looking to identify and develop VEGF antagonists that required more infrequent administrations to treat patients with vasogenic eye disorders because “[a] decrease in the number of injections would reduce the potential risk of injection-related complications, and an increase in the injection-free interval would reduce the burden of frequent follow-up evaluations.” Ex. 1045 at 16-18. *See also*, Ex. 1007 at 5 (each intravitreal injection “subjects patients to risk of cataract, intraocular inflammation, retinal detachment, and endophthalmitis.”); Ex.2025 at 634 (“many clinicians and patients are reluctant to commit to a strategy of 24 [intravitreal] injections in the first two years of

treatment.”). Intravitreal injections also subject patients to significant pain and discomfort.

249. Moreover, “[t]he time and financial burden of monthly injections [such as with ranibizumab and bevacizumab] has led to the initiation of studies to examine the efficacy of alternative dosing schedules.” Ex. 1007 at 2. Unfortunately, “studies seem[ed] to indicate that quarterly dosing [of ranibizumab] is associated with poorer outcomes” and that “even with the p.r.n. dosing ... patients are still required to make monthly visits to the office with frequent and expensive testing.” *Id.* Dixon noted that “limitations of current therapy include the need for frequent intraocular injections, as often as monthly, without a defined stopping point.” Ex. 1007 at 5. Thus, “[d]esireable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and decreased dosing intervals.” *Id.*

250. Even before 2011, VEGF Trap-Eye/aflibercept had been recognized as “represent[ing] the most promising anti-VEGF investigational drug that is currently in Phase III trial.” *Id.* It was also recognized that “[i]n contrast to current anti-VEGF antibodies, which are rapidly cleared, the VEGF-VEGF Trap complex is relatively inert, and is degraded more slowly. Due to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye.” *Id.* “Predictive modeling studies [also] indicate[d] that VEGF

Trap-Eye should have a longer duration of activity than currently available treatments.” Ex. 1016 at 1.

251. Thus, as of 2011, VEGF Trap-Eye/aflibercept was the subject of extensive studies to evaluate its efficacy with less frequent dosing. The results from those studies would have provided POSAs with an expectation that VEGF Trap-Eye/aflibercept could be administered relatively infrequently. For example, in the CLEAR-IT 2 trial, “[p]atients were randomized into 5 groups (N=195 randomized, N=157 treated) and treated with VEGF Trap-Eye in the study at 0.5 mg and 2.0 mg [every 4 weeks], and 0.5, 2.0 and 4.0 [every 12 weeks] for 12 weeks, followed by as needed)prn) dosing through week 52.” Ex. 1016 at 2. “After the last fixed-dose administration at week 12, patients from all dose groups required on average only *one additional injection over the following 20 weeks* to maintain visual acuity gain achieve” (Ex. 1008 at 268 (emphasis added)) and “patients from all dose groups combined received, on average, *only 2 additional injections*” for the entire prn period from week 12 to week 52. Ex. 1016 at 5 (emphasis added). Notably, “[f]ifty-five percent of patients receiving 2.0 mg monthly for 12 weeks *did not require any additional treatment* through the next 20-week PRN dosing period.” Ex. 1008 at 8 (emphasis added).

252. The above data would have motivated a POSA to at least try to administer a single 2.0 mg or 0.5 mg initial dose followed by monthly doses with

the reasonable expectation that over time monthly dosing would no longer be necessary for the treatment of diabetic retinopathy and DME. Ex. 1007 at 4 (emphasis added). Further, in view of the dosing regimen from the VIEW 1 and VIEW 2 studies, as disclosed in the prior art, a POSA would be motivated to administer aflibercept no more frequently than every 12 weeks for the treatment of diabetic retinopathy and DME after an initial period of monthly dosing.

253. Moreover, a POSA would have understood that in at least some diabetic retinopathy and DME patients, administration of 2.0 mg or 0.5 mg aflibercept on a monthly basis followed by administration once every 12 weeks would be optimal in the treatment of at least some diabetic retinopathy and DME patients. In fact, traditionally, administration of VEGF-antagonists for the treatment of DME has been on as needed basis. Thus, in all of the studies discussed herein, there is a p.r.n. dosing period after a fixed monthly dosing period. This is because, not all patients respond the same to treatment. For example, as discussed above, in the CLEAR-IT 2 study, while fifty-five percent of patients receiving 2.0 mg monthly for 12 weeks did not require any additional treatment for a 20-week period after a 3month fixed dosing period, the other 45 percent of patients required a different dosing schedule. Ex. 1008 at 8. As such, there would be at least some patients in whom administration every 12 weeks will be effective after an initial monthly administration period.

B. NCT-795 (Ex. 1017) INVALIDATES THE CHALLENGED CLAIMS

1. Claim 1 is Anticipated by NCT-795

a) “A method for treating an angiogenic eye disorder in a patient, said method”

254. NCT-795 discloses an “Investigation Efficacy and Safety in Wet Age-Related Macular Degeneration.” Ex. 1017 at 1, 3, 4. As of 2011, a POSA would have known that “wet age-related macular degeneration” is a type of angiogenic eye disorder. Moreover, a POSA would have understood that a study involving administration of a drug for the treatment of wet AMD would require a methods of treatment.

255. Therefore, NCT-795 discloses a method for treating an angiogenic eye disorder in a patient.

b) “comprising sequentially administering to the patient a single initial dose of VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of VEGF antagonist”

256. NCT-795 discloses at least two “Assigned Interventions” for the VIEW1 study that meet this limitation:

- “0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year.

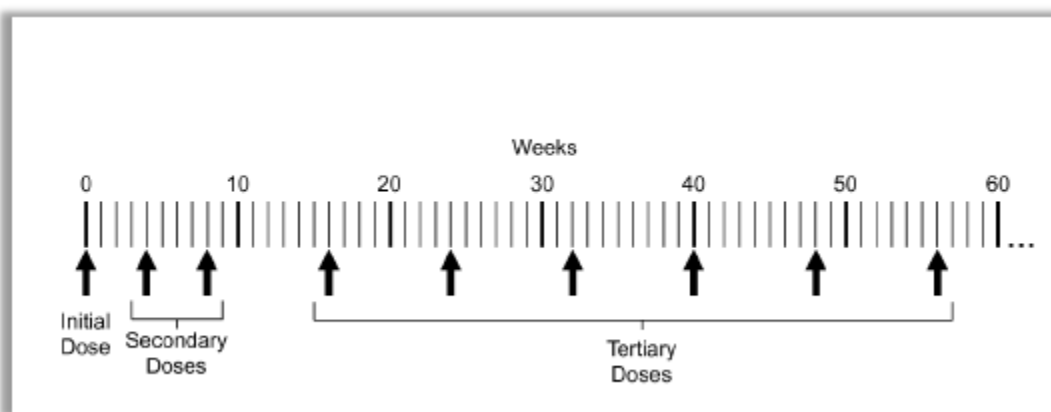
Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” (Ex. 1017 at 6)

- “2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year.

Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” (Ex. 1017 at 7)

257. A POSA reviewing the specification for the '345 patent including Figure 1 would understand that, pursuant to the NCT-795 “Assigned Interventions,” (i) the first 0.5 mg or 2.0 mg VEGF Trap-Eye/aflibercept administration would be the claimed “single initial dose” of VEGF Trap-Eye/aflibercept; and (ii) the doses after the single initial dose that are administered “every 4 weeks during the first year” would be “one or more secondary doses.”

258. The '345 patent state that FIG. 1 “shows an exemplary dosing regimen of the present invention.” Ex. 1001 at 2:63-64. I provide FIG. 1 from the '345 patent below for reference:



The '345 patent further explains that “[i]n this regimen, a single ‘initial dose’ of VEGF antagonist ... is administered at the beginning of the treatment regimen (i.e., at week 0), two ‘secondary doses’ are administered at weeks 4 and 8, respectively.”

Id. at 2:64-67. Similarly, in the VIEW 1 study as disclosed in NCT-795, the first dose, which would necessarily have to be at 0 weeks—i.e., at the very start of the study—is the “initial dose.” The dose immediately following the dose at 0 weeks would therefore then be the start of any “secondary doses.” And in the case of the “Assigned Interventions” disclosed in NCT-795, the doses administered “every four weeks for the first year” after the first initial dose at week 0 would be the claimed “one or more secondary doses.”

259. Finally, a POSA would understand that doses administered after the first year would be the claimed tertiary dose as these doses do not necessarily have to be every 4 weeks as required during the first year of the “Assigned Intervention” but instead may be “no less frequent[] than every 12 weeks”—meaning they can, in fact, be as infrequent as every 12 weeks.

260. Therefore, NCT-795 discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist.

c) “wherein each secondary dose is administered 4 weeks after the immediately preceding dose”

261. As I have explained above, a POSA would understand that, pursuant to the “Assigned Interventions” disclosed in NCT-795, the doses after the single initial

dose that are administered—i.e., “every 4 weeks during the first year” would be “one or more secondary doses,” and these doses would be administered after the immediately preceding initial dose.

262. Therefore, discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

d) “wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.”

263. As I have explained above, a POSA would understand that, pursuant to the “Assigned Interventions” disclosed in NCT-795, doses administered after the first year would be the claimed tertiary dose and that these doses may be “no less frequent[] than every 12 weeks”—meaning they can, in fact, be as infrequent as every 12 weeks, including 12 weeks after the final “secondary dose” at the end of the first year.

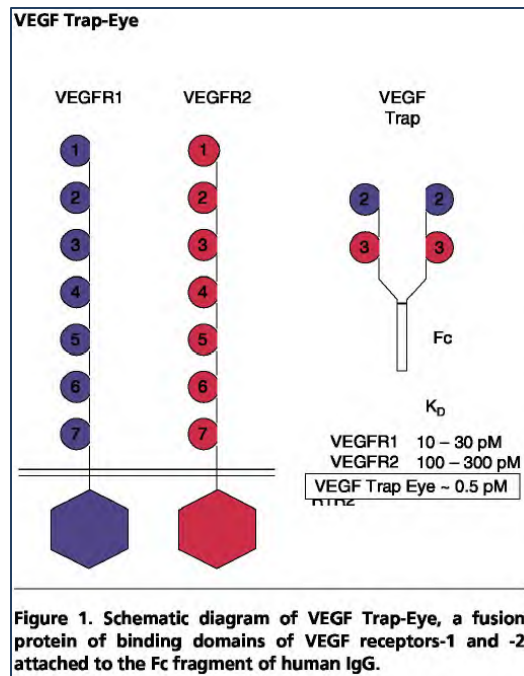
264. Therefore, discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF

antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.”

- e) **“wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1 and a multimerizing component.”**

265. A POSA would understand this limitation is merely a recitation of the domain composition of aflibercept/VEGF Trap-Eye disclosed in NCT-795. This was well known long before 2011. As such the VEGF Trap-Eye disclosed in NCT-795 inherently meets this limitation.

266. Dixon disclosed that “[s]tructurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment” and provides the below Figure:



Ex. 1007 at 1575; Fig. 1.; Ex. 1005 at 1-2 (disclosing ““VEGF-Trap_{R1R2} was created by fusing a second Ig domain of VEGFR1 with the third Ig domain of VEGFR2.”); Ex. 1032 at 3 (disclosing “a chimeric fusion protein containing a modified domain 2 of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc region of human IgG1, resulting in a fully human protein that we term VEGF Trap.”); Ex. 1033 at 2 (disclosing that “VEGF Trap is a recombinant soluble VEGF receptor protein in which the binding domains of VEGF receptors 1 and 2 are combined with the Fc portion of immunoglobulin G.”); Ex. 1034 at 18363 (disclosing that “VEGF Trap is a fully human soluble decoy receptor protein that consists of a fusion of the second Ig domain of human VEGF receptor (VEGFR) 1 and the third Ig domain of human VEGFR2 with the constant region (Fc) of human Ig IgG1.”); Ex. 1035 at 4 (disclosing “[VEGF Trap] was designed to bind VEGF with exceedingly high-

affinity. The VEGF Trap is a soluble chimeric receptor in which key domains of VEGFR1 (domain 2) and VEGFR2 (domain 3) are fused to the constant region (Fc portion) of human IgG1 [34]. This fully human protein is capable of binding all isoforms of VEGF-A with very high affinity ($K_D < 0.5$ pM for hVEGF165). Moreover, and in contrast to antibodies directed against VEGF-A, the VEGF Trap also binds PlGF, a VEGF family member also implicated in pathological angiogenesis [46] ($K_D \sim 25$ pM for hPlGF2).); Ex. 1037 at 18 (Regeneron disclosing its clinical study program for aflibercept which it identifies as “VEGF Trap.”); Ex. 1012 at Fig.234A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the Fc Δ C1 domain)), 10:15-17 (specifying that this molecule is termed “VEGFR1R2-Fc Δ C1(a).”); Ex. 1008 at 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug.”).

267. Therefore, NCT-795 discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after

the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.

2. Claim 2 is Anticipated by NCT-795

268. Claim 2 of the '345 patent depends from claim 1. Therefore, I incorporate my opinions with respect to claim 1 herein. Claim 2 further requires “wherein the VEGF antagonist is aflibercept.”

269. As discussed above with respect to claim 1, VEGF Trap-Eye. For reasons set forth above in Section VIII.C of this Declaration, VEGF Trap-Eye is necessarily aflibercept and as such, NCT-795 inherently discloses aflibercept.

270. Therefore, NCT-795 discloses the method of claim 1, wherein the VEGF antagonist is aflibercept.

3. Claims 3-4 Are Anticipated by NCT-795

271. Claims 3 and 4 ultimately depend from claim 1. Therefore, I incorporate my opinions with respect to claim 1 herein. Claims 3 and 4 further require “wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration” (claim 3) and “wherein the intraocular administration is intravitreal administration” (claim 4).

272. NCT-795 discloses Phase III study with an “Official Title”: “A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of *Intravitreal VEGF Trap* in Subjects With Neovascular Age-Related Macular Degeneration.” Ex. 1017 at 3 (emphasis added).

273. Therefore, NCT-795 discloses the method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration (claim 3) and wherein the intraocular administration is intravitreal administration (Claim 4).

4. Claims 5-7 Are Anticipated by NCT-795

274. Claims 5-7 depend from claim 4. Therefore, I incorporate my opinions with respect to claim 4 herein. Claims 5, 6, and 7 also require “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist” (claim 5); “wherein all doses ... comprise 0.5 mg of the VEGF antagonist” (claim 6); and “wherein all doses ... comprise 2 mg of the VEGF antagonist (claim 7).

275. As discussed above with respect to claim 1, NCT-795 recites several study groups including a 0.5 mg dose and a 2.0 mg dose “administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.” Ex. 1017 at 6, 7.

276. Therefore, NCT-795 discloses the method of claim 4, “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist” (claim 5); “wherein all doses ... comprise 0.5 mg of the VEGF antagonist” (claim 6); and “wherein all doses ... comprise 2 mg of the VEGF antagonist” (claim 7).

5. Claims 8 and 9 Are Anticipated by NCT-795

277. Claims 8 and 9 depend from claim 5. Therefore, I incorporate my opinions with respect to claim 5 herein. Claims 8 and 9 also require “wherein the angiogenic eye disorder is selected from the group, consisting of: age related macular degeneration, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization” (claim 8); and “wherein the angiogenic eye disorder is age related macular degeneration” (claim 9).

278. As discussed above with respect to claim 1, NCT-795 discloses a method of administering VEGF Trap-Eye for the treatment of “wet age-related macular degeneration (AMD).” Ex. 1017 at 3.

279. Therefore, NCT-795 discloses the method of claim 5, “wherein the angiogenic eye disorder is selected from the group, consisting of: age related macular degeneration, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization” (claim 8); and “wherein the angiogenic eye disorder is age related macular degeneration” (claim 9).

6. Claims 10 and 11 are Obvious Over NCT-795 in view of Regeneron (18-Feb-2010) and a POSA's Knowledge

280. Claims 10 and 11 depend from claim 8. Therefore, I incorporate by opinions with respect to Claim 8 herein. Claims 10 and 11 also require “wherein the angiogenic eye disorder is diabetic retinopathy” (claim 10) and “wherein the angiogenic eye disorder is diabetic macular edema (claim 11).

281. For reasons set forth above in Section XI.A.6 of this Declaration, it is my opinion that claims 10 and 11 of the '345 patent are obvious over NCT-795 in view of Regeneron (18-Feb-2010) and a POSA's knowledge. Specifically, in my opinion, a POSA as of 2011 would have been motivated with a reasonable expectation of success to apply the dosing regimen disclosed in NCT-795 to the treatment of diabetic macular edema (and therefore also diabetic retinopathy) in view of the positive Phase II study data disclosed in Regeneron (18-Feb-2010), and a POSA's knowledge that (i) VEGF plays a major role in the pathogenesis of vasogenic eye disorders, including AMD, diabetic retinopathy and diabetic macular edema; (ii) VEGF antagonists had been shown to be effective in the treatment of vasogenic eye disorders; and (iii) VEGF Trap-Eye/aflibercept was a known VEGF-antagonist that had been shown to be effective in treating diabetic retinopathy with less frequent administration.

282. Moreover, a POSA would have understood that in at least some diabetic retinopathy and DME patients, administration of 2.0 mg or 0.5 mg aflibercept on a

monthly basis followed by administration once every 12 weeks would be optimal in the treatment of at least some diabetic retinopathy and DME patients.

C. REGENERON (8-MAY-2008) (EX. 1022) INVALIDATES THE CHALLENGED CLAIMS

1. Claim 1 is Anticipated by Regeneron (8-May-2008)

a) “A method for treating an angiogenic eye disorder in a patient”

283. Regeneron (8-May-2008) is 2008 press release issued by Regeneron. It discloses information about the “VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of neovascular form of Age related Macular Degeneration (wet AMD), a leading cause of blindness in adults.” Ex. 1022 at 1. As of 2011, a POSA would have known that “wet age-related macular degeneration” is a type of angiogenic eye disorder. Moreover, a POSA would have understood that a study involving administration of a drug for the treatment of wet AMD would require a methods of treatment.

284. Therefore, Regeneron (8-May-2008) discloses “a method for treating an angiogenic eye disorder in a patient.”

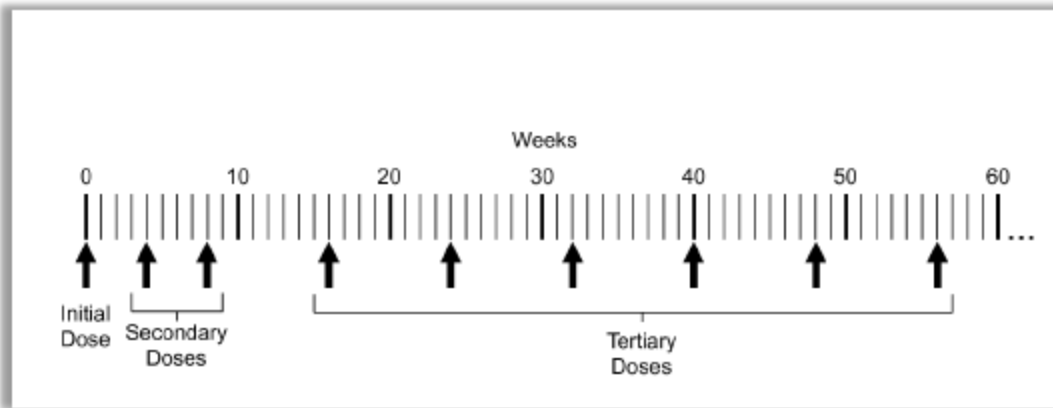
b) “comprising sequentially administering to the patient a single initial dose of VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of VEGF antagonist”

285. Regeneron (8-May-2008) discloses that “[i]n the first year, the VIEW 2 ... study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5

milligrams (mg) and 2.0 mg administered at 4 week intervals.” *Id.* at 1. Thus, Regeneron (8-May-2008) discloses at least two study groups: one in which patients will receive a 0.5 mg dose every 4 weeks for a year and another in which patients will receive a 2.0 mg dose of VEGF Trap-Eye every 4 weeks for a year. Regeneron (8-May-2008) further discloses that in each of these groups “[a]fter the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based regimen with a dose administered at least every 12 weeks, but not more often than every 4 weeks until the end of the study.” *Id.*

286. A POSA reviewing the specification for the ’345 patent including Figure 1 would understand that, pursuant to the dosing regimens that would be administered to patients in the VIEW 2 study as disclosed in Regeneron (8-May-2008): (i) the first 0.5 mg or 2.0 mg VEGF Trap-Eye/aflibercept administration would be the claimed “single initial dose” of VEGF Trap-Eye/aflibercept; and (ii) the doses after the single initial dose that are administered “every 4 weeks for a year” would be “one or more secondary doses.”

287. The ’345 patent state that FIG. 1 “shows an exemplary dosing regimen of the present invention.” Ex. 1001 at 2:63-64. I provide FIG. 1 from the ’345 patent below for reference:



The '345 patent further explains that “[i]n this regimen, a single ‘initial dose’ of VEGF antagonist ... is administered at the beginning of the treatment regimen (i.e., at week 0), two ‘secondary doses’ are administered at weeks 4 and 8, respectively.” *Id.* at 2:64-67. Similarly, in the VIEW 2 study as disclosed in the Regeneron (8-May-2008), the first dose, which would necessarily have to be at 0 weeks—i.e., at the very start of the study—is the “initial dose.” The dose immediately following the dose at 0 weeks would therefore then be the start of any “secondary doses.” And in the case of the VIEW 2 as disclosed in the Regeneron (8-May-2008), the doses administered “every four weeks for a year” after the first initial dose at week 0 would be the claimed “one or more secondary doses.”

288. Finally, a POSA would understand that doses administered after the first year would be the claimed tertiary dose as these doses do not necessarily have to be every 4 weeks as required during the first year of the VIEW 2 study but instead may be “administered at least every 12 weeks”—meaning they can, in fact, be as infrequent as every 12 weeks.

289. Therefore, the Regeneron (8-May-2008) discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist.

c) “wherein each secondary dose is administered 4 weeks after the immediately preceding dose”

290. As I have explained above, a POSA would understand that, pursuant to the disclosures regarding VIEW 2 in Regeneron (8-May-2008), the doses after the single initial dose that are administered—i.e., “every 4 weeks for a year” would be “one or more secondary doses,” and these doses would be administered after the immediately preceding initial dose.

291. Therefore, Regeneron (8-May-2008) discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose.

d) “wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.”

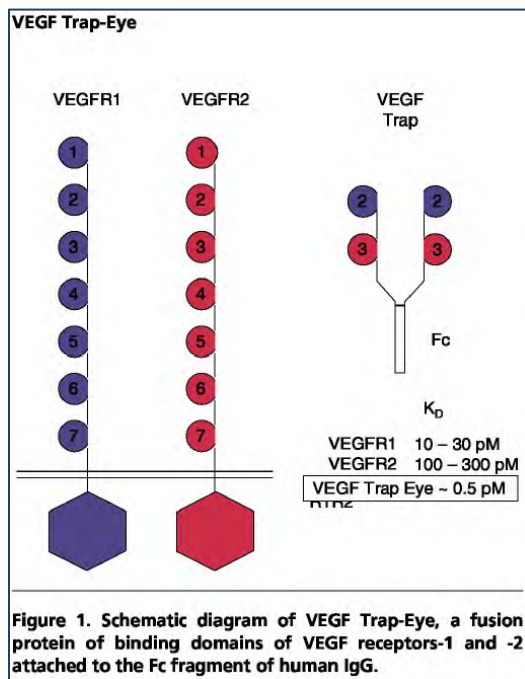
292. As I have explained above, a POSA would understand that, pursuant to the disclosures regarding VIEW 2 in Regeneron (8-May-2008), doses administered after the first year would be the claimed tertiary dose and that these doses may be “administered at least every 12 weeks”—meaning they can, in fact, be as infrequent as every 12 weeks, including 12 weeks after the final “secondary dose” at the end of the first year.

293. Therefore, Regeneron (8-May-2008) discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.

- e) **“wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1 and a multimerizing component.”**

294. A POSA would understand this limitation is merely a recitation of the domain composition of aflibercept/VEGF Trap-Eye disclosed in NCT-795. In fact, this was well known long before 2011. As such the VEGF Trap-Eye disclosed in NCT-795 inherently meets this limitation.

295. Dixon disclosed that “[s]tructurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment” and provides the below Figure:



Ex. 1007 at 3; Fig. 1.; Ex. 1005 at 1-2 (disclosing ““VEGF-Trap_{R1R2} was created by fusing a second Ig domain of VEGFR1 with the third Ig domain of VEGFR2.”); Ex. 1032 at 3 (disclosing “a chimeric fusion protein containing a modified domain 2 of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc region of human IgG1, resulting in a fully human protein that we term VEGF Trap.”); Ex. 1033 at 1522.e2 (disclosing that “VEGF Trap is a recombinant soluble VEGF receptor protein in which the binding domains of VEGF receptors 1 and 2 are combined with the Fc portion of immunoglobulin G.”); Ex. 1034 at 1 (disclosing that “VEGF Trap is a fully human soluble decoy receptor protein that consists of a fusion of the second Ig

domain of human VEGF receptor (VEGFR) 1 and the third Ig domain of human VEGFR2 with the constant region (Fc) of human Ig IgG1.”); Ex. 1035 at 416 (disclosing “[VEGF Trap] was designed to bind VEGF with exceedingly high-affinity. The VEGF Trap is a soluble chimeric receptor in which key domains of VEGFR1 (domain 2) and VEGFR2 (domain 3) are fused to the constant region (Fc portion) of human IgG1 [34]. This fully human protein is capable of binding all isoforms of VEGF-A with very high affinity (KD <0.5 pM for hVEGF165). Moreover, and in contrast to antibodies directed against VEGF-A, the VEGF Trap also binds PlGF, a VEGF family member also implicated in pathological angiogenesis [46] (KD ~25 pM for hPlGF2)”); Ex. 1037 at 18 (Regeneron disclosing its clinical study program for aflibercept which it identifies as “VEGF Trap.”); Ex. 1012 at Fig.234A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain)), 10:15-17 (specifying that this molecule is termed “VEGFR1R2-FcΔC1(a).”); Ex. 1008 at 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug.”).

296. Therefore, Regeneron (8-May-2008) discloses a method for treating an angiogenic eye disorder in a patient, said method comprising sequentially

administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 12 weeks after the immediately preceding dose; wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.”

2. Claim 2 is Anticipated by Regeneron (8-May-2008)

297. Claim 2 of the '345 patent depends from claim 1. Therefore, I incorporate my opinions with respect to claim 1 herein. Claim 2 further requires “wherein the VEGF antagonist is aflibercept.”

298. As discussed above with respect to claim 1, VEGF Trap-Eye. For reasons set forth above in Section VIII.C of this Declaration, VEGF Trap-Eye is necessarily aflibercept and as such, NCT-795 inherently discloses aflibercept.

299. Therefore, Regeneron (8-May-2008) discloses the method of claim 1, wherein the VEGF antagonist is aflibercept.

3. Claims 3-4 Are Anticipated by Regeneron (8-May-2008)

300. Claims 3 and 4 ultimately depend from claim 1. Therefore, I incorporate my opinions with respect to claim 1 herein. Claims 3 and 4 further

require “wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration” (claim 3) and “wherein the intraocular administration is intravitreal administration” (claim 4).

301. Regeneron (8-May-2008) discloses “Both VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by *intravitreal injection*.” Ex. 1022 at 1 (emphasis added).

302. Therefore, Regeneron (8-May-2008) discloses the method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration (claim 3) and wherein the intraocular administration is intravitreal administration (Claim 4).

4. Claims 5-7 Are Anticipated by Regeneron (8-May-2008)

303. Claims 5-7 depend from claim 4. Therefore, I incorporate my opinions with respect to claim 4 herein. Claims 5, 6, and 7 also require “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist” (claim 5); “wherein all doses ... comprise 0.5 mg of the VEGF antagonist” (claim 6); and “wherein all doses ... comprise 2 mg of the VEGF antagonist (claim 7).

304. As discussed above with respect to claim 1, Regeneron (8-May-2008) recites several study groups including a 0.5 mg dose and a 2.0 mg dose “administered

at 4 week intervals” during the first year. Ex. 1022 at 1. Thereafter a dose may be administered “at least every 12 weeks.” Ex. 1017 at 6, 7.

305. Therefore, Regeneron (8-May-2008) discloses the method of claim 4, “wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist” (claim 5); “wherein all doses ... comprise 0.5 mg of the VEGF antagonist” (claim 6); and “wherein all doses ... comprise 2 mg of the VEGF antagonist” (claim 7).

5. Claims 8 and 9 Are Anticipated by Regeneron (8-May-2008)

306. Claims 8 and 9 depend from claim 5. Therefore, I incorporate my opinions with respect to claim 5 herein. Claims 8 and 9 also require “wherein the angiogenic eye disorder is selected from the group, consisting of: age related macular degeneration, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization” (claim 8); and “wherein the angiogenic eye disorder is age related macular degeneration” (claim 9).

307. As discussed above with respect to claim 1, Regeneron (8-May-2008) discloses a method of administering VEGF Trap-Eye for the treatment of “wet AMD.” Ex. 1017 at 1.

308. Therefore, Regeneron (8-May-2008) discloses the method of claim 5, “wherein the angiogenic eye disorder is selected from the group, consisting of: age related macular degeneration, diabetic macular edema, central retinal vein occlusion,

branch retinal vein occlusion, and corneal neovascularization” (claim 8); and “wherein the angiogenic eye disorder is age related macular degeneration” (claim 9).

6. Claims 10 and 11 are Obvious Over Regeneron (8-May-2008) in view of Regeneron (18-Feb-2010) and a POSA’s Knowledge

309. For reasons set forth above in Section XI.A.6 of this Declaration, it is my opinion that claims 10 and 11 of the ’345 patent are obvious over Regeneron (8-May-2008) in view of Regeneron (18-Feb-2010) and a POSA’s knowledge. In particular, a POSA as of 2011 would have been motivated with a reasonable expectation of success to apply the dosing regimen disclosed in Regeneron (8-May-2008) to the treatment of diabetic macular edema (and therefore also diabetic retinopathy) in view of the positive Phase II study data disclosed in Regeneron (18-Feb-2010), and a POSA’s knowledge that (i) VEGF plays a major role in the pathogenesis of vasogenic eye disorders, including AMD, diabetic retinopathy and diabetic macular edema; (ii) VEGF antagonists had been shown to be effective in the treatment of vasogenic eye disorders; and (iii) VEGF Trap-Eye/aflibercept was a known VEGF-antagonist that had been shown to be effective in treating diabetic retinopathy with less frequent administration.

310. Moreover, a POSA would have understood that in at least some diabetic retinopathy and DME patients, administration of 2.0 mg or 0.5 mg aflibercept on a

monthly basis followed by administration once every 12 weeks would be optimal in the treatment of at least some diabetic retinopathy and DME patients.

XII. SECONDARY CONSIDERATIONS

311. I understand that a patent owner may in some circumstances rely on so called “secondary considerations of non-obviousness” to attempt to refute a finding of obviousness of a claim. In this case, the only claims to which any such evidence would be applicable are claims 10 and 11 since those are the only claims for which I provide obviousness opinions.

312. I also understand that there are several categories of secondary considerations, which might include alleged unexpected results or a “long-felt but unmet need.” Notwithstanding that the unpatentability of the challenged claims is supported by strong evidence, including the numerous Regeneron public announcements and prior art disclosure of the claimed dosing regimen for VEGF Trap-Eye/aflibercept well prior to the filing date of the ’345 patent, it is my opinion that there are no unexpected results or a “long-felt but unmet need” that would refute the strong case of obviousness against claims 10 and 11.

313. To the extent that Regeneron asserts unexpected results were obtained after administering aflibercept for the treatment of diabetic retinopathy or DME, I disagree. As I discussed above, there were ample reasons for why POSAs reasonably expected positive results from administering VEGF Trap-

Eye/aflibercept according to the method disclosed in Dixon, NCT-377, NCT-975, and Regeneron (8-May-2008). To begin with, AMD and diabetic retinopathy share a common pathogenesis with respect to angiogenesis resulting from VEGF. *See, e.g.,* Ex. 1037 at 19 (“Wet AMD and diabetic retinopathy (which includes DME) are two of the leading causes of adult blindness in the developed world. In both conditions, severe visual loss is caused by a combination of retinal edema and neovascular proliferation.”). The purpose of administering VEGF Trap-Eye/aflibercept is to inhibit the VEGF process in the treatment of AMD, diabetic retinopathy and DME. As such, positive results from the administration of VEGF Trap-Eye/aflibercept for the treatment of AMD is also relevant to and supports the POSA’s expectation that there will also be positive results for the treatment of diabetic retinopathy and DME.

314. In fact, as of the 2011, the prior art disclosed positive results from the administration of VEGF Trap-Eye/aflibercept for the treatment of DME. *See, e.g.,* ¶¶ 240-242, above. Additionally, there were “preclinical results [that] support a role ... in particular for local delivery of VEGF Trap, in multiple vascular eye diseases ranging from AMD and diabetic eye diseases to corneal injury and transplantation.” Ex. 1032 at 4. More importantly, positive results for the treatment of diabetic retinopathy in human patients were also disclosed as of the priority date of the ’345 patent. In an open-label study for the treatment of diabetic macular edema (DME)

in which “a single [VEGF Trap-Eye intravitreal] injection [of 4 mg] resulted in a median decrease of central macular thickness measured by OCT of 79 μm ” and BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks.” Ex. 1007 at 4. *See also*, Ex. 1032 at 4-5 (“Initial clinical studies in human patients suffering both AMD and diabetic edema and retinopathy appear quite promising, with evidence in early trails that VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity.”).

315. Regeneron’s decision in 2009 to conduct a Phase II study to confirm VEGF Trap-Eye/aflibercept’s usefulness for the treatment of diabetic retinopathy further evidences the POSA’s expectations. Ex. 1037 at 19 (“We and Bayer HealthCare also are conducting a Phase 2 study of VEGF Trap-Eye in patients with diabetic macular edema (DME).”). Accordingly, in light of the positive results from pre-clinical and clinical studies and the knowledge regarding the pathogenesis of diabetic retinopathy, there is nothing unexpected from the administration of VEGF Trap-Eye/aflibercept according to the claimed dosing regimen.

316. Second, in my experience as a person of ordinary skill in the art, as of 2011, monthly dosing was not the sole regimen typically used in standard clinical practice. By 2011, as I discuss above, the discomfort, inconvenience, and risks experienced by patients receiving intravitreal injections led most in the

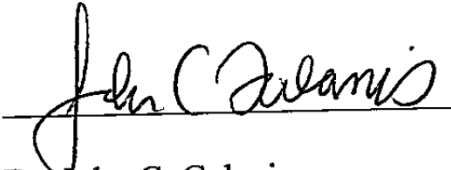
ophthalmology community to resort to p.r.n. or as-needed dosing to reduce the frequency of administration whenever possible. For example, my typical practice, together with the typical practice of the skilled person, administering intravitreal anti-VEGF agents involved the administration of a few loading dose injections, typically spaced a month apart. Thereafter, we would usually bring back patients for monthly visits to assess visual acuity and retinal swelling and only administer injections on those monthly visits where there appeared to be loss in visual acuity or increase in retinal swelling. Thus, should Regeneron attempt to characterize the standard of care at the relevant time as monthly dosing to argue the purported unexpectedness of the results from the claimed every-twelve-week dosing regimen, this would ignore the actual real-world practice of ophthalmologists.

317. Moreover, to the extent that the inventors would claim an unmet and long-felt need was fulfilled with the '345 patent, in my opinion, this is not the case. While I agree that there may have been a need for VEGF antagonists prior to their development, in my opinion, once those antagonists were developed, and especially after the dosing knowledge was gleaned from ranibizumab and the early trials of VEGF Trap-Eye, arriving at a dosing regimen that extended the administration beyond once-monthly was obvious, had already been noted in the literature and put into actual practice, and served no "unmet" need. This is particularly so given that the dosing regimen was already publicly disclosed as early as 2009, meaning that

any “unmet” need had already been met by Regeneron’s own public disclosures well before the ’345 priority application(s) was filed.

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

Dated: 7/9/2025

By: 
Dr. John C. Galanis