

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALVOTECH USA INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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

DECLARATION OF DONALD JOSEPH D'AMICO

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I, Donald Joseph D'Amico, M.D., declare as follows:

I. QUALIFICATIONS AND BACKGROUND INFORMATION

1. My curriculum vitae is attached hereto as Appendix A. I highlight my educational background, career history, publications, and other relevant qualifications in summary below.

2. Over the past nearly 45 years, I have dedicated my medical career to treating patients, research, and teaching in ophthalmology. I specialize in the care of patients with vitreoretinal surgical diseases and medical retinal diseases including angiogenic eye disorders with particular emphasis on the treatment of patients with wet age-related macular degeneration, diabetic retinopathy, diabetic macular edema, and other like conditions. Over the course of decades of treating patients, I have had the opportunity to utilize different treatment options for patients with vitreoretinal and angiogenic eye disorders, including anti-VEGF intravitreal injections. I have experience treating patients with all the currently available anti-VEGF treatments, including off-label Avastin® (bevacizumab), Lucentis® (ranibizumab), Eylea® (aflibercept, 2 mg and 4 mg) and Eylea HD® (aflibercept, 8 mg), and Vabysmo® (faricimab 6 mg).

3. In 1972, I received a Bachelor of Science degree in chemistry from Massachusetts Institute of Technology. Following my undergraduate studies, I received a Doctor of Medicine degree (M.D.) from the University of Illinois College of Medicine in 1977. After receiving my M.D., I completed my post-doctoral internship at Michael Reese Hospital in Chicago, IL from 1977 to 1978. I then completed my residency in ophthalmology from 1978 to 1981 at Massachusetts Eye and Ear Infirmary which is the primary teaching hospital of Harvard Medical School's Department of Ophthalmology. Following my residency, I completed a fellowship in vitreoretinal diseases at Bascom Palmer Eye Institute of the University of Miami from 1981 to 1982.

4. I currently practice medicine at Weill Cornell Medical College where I hold several positions. Since 2006, I have served as Professor and Chairman of the Israel Englander Department of Ophthalmology and practiced as an attending physician in the Retina Service. In 2014, I was also appointed as the distinguished John Milton McLean Professor of Ophthalmology. Since 2006, I have also served as the Ophthalmologist-in-Chief and attending physician at New York Presbyterian Hospital.

5. Prior to these positions, I held academic roles including patient care, teaching and performing research at Harvard Medical School from 1982 to 2006. Most notably, I served as Professor of Ophthalmology at Harvard from 1999 to 2006. I also held various clinical roles at the Massachusetts Eye and Ear Infirmary from 1982 to 2006 including Assistant Chief of Ophthalmology from 1990 to 2006 and Director of the Diabetic Retinopathy Unit from 1982 to 2006. During that time, I twice received the Teacher of the Year Award given by the residents of the Massachusetts Eye and Ear Infirmary for my instruction of medical students, ophthalmology residents, and retina fellows.

6. I am currently certified by the American Board of Ophthalmology and have been since 1982. I have been licensed to practice in New York since 2006 and previously held a license to practice in Massachusetts from 1981 to 2007.

7. Research has been a substantial part of my career. I served as the Director of the Margaret M. Dyson Vision Research Institute at Weill Cornell Medical College within the Department of Ophthalmology from 2006 to 2010 then again from 2015 to the present. I have been a Principal Investigator or co-investigator on nearly 20 clinical trials and laboratory investigations involving eye disorders including diabetic retinopathy and neovascular age-related macular

degeneration. Early in my career, I was principal investigator on two successfully completed NIH grants that examined the effects of the intravitreal toxicity of injected antibiotics on the retina; these studies were performed on experimental animals and utilized electron microscopy to determine the presence of damaging effects on the delicate retinal tissues. Throughout my career, I have authored or co-authored over 175 peer-reviewed papers, co-edited two books and authored or co-authored over 65 book chapters related to vitreoretinal and angiogenic eye disorders, including anti-VEGF intravitreal injections.

8. I have been recognized as a national and international lecturer and have been the recipient of nearly 50 honors and awards. These include the Senior Achievement Award and the Honor Award from the American Academy of Ophthalmology, the Gertrude Pyron Award of the American Society of Retinal Specialists, and the J. Donald M. Gass Medal Lecture Award of the Retina Society.

9. I currently serve on the editorial boards of three major journals. From 2016 to 2023, I was the Inaugural Editor-in-Chief for the Journal of VitreoRetinal Diseases. I've also served on the board for Seminars in Ophthalmology and Ophthalmic Surgery, Lasers, and Imaging since 1990 and 1995 respectively.

Previously, I served on the editorial board of Retina for 25 years and on the board for the Digital Journal of Ophthalmology for 6 years.

10. I am also active in professional societies. I am involved in Club Jules Gonin, the international retinal society, where I began as a member in 1992, served on the Abstract Review and Program Committee from 2002 to the present, served on the Executive Committee from 2004 to the present and served as President from 2009 to 2012. Similarly, I have also been a member of the Aspen Retinal Detachment Society since 1982 and served as the Program Chair since 2000. I have been active in the Retina Society where I first became a member in 1986, Secretary in 2000, Vice-President in 2005, and President from 2007 to 2009. I have also been a fellow at the American Academy of Ophthalmology from 1982 to the present and a fellow at The New York Clinical Society from 2007 to the present. I have also been a member in approximately 20 other notable organizations focused on ophthalmology such as the Association for Research in Vision and Ophthalmology, New England Ophthalmological Society, Macula Society, Association of University Professors of Ophthalmology, and the New York Ophthalmological Society.

II. COMPENSATION

11. I am being compensated at my customary rate of \$1,000 per hour for my work in this matter. I am also being reimbursed for reasonable travel expenses related to my consultation. My compensation is in no way based on the outcome of this matter and has not influenced my views in this matter.

III. MATERIALS CONSIDERED

12. In writing this Declaration, I have relied on my background, education, and experience as physician, both in treating patients with angiogenic eye disorders and studying the treatment of such disorders in clinical trials. I also rely upon a discussion with Dr. Robert Falconer that took place on June 16, 2025. I have also considered, in whole or in part, the following documents in forming my opinion in this matter.

Exhibit	Description
1001	U.S. Patent No. 12,168,036 (Graham et al.)
1002	File History for U.S. Patent No. 12,168,036
1004	Declaration of Dr. Robert J. Falconer
1005	U.S. Patent No. 7,608,261 (Furfine)
1006	U.S. Patent No. 8,921,316 (Dix)
1007	U.S. Publication No. 2016/0144025 A1 (Vitti)
1008	Center for Drug Evaluation and Research, “Clinical Pharmacology and Biopharmaceutics Review(s)” App. No. 125387Orig1s000 (2011) (“2011 Eylea® Clinical Review”)
1009	Product Information EYLEA® aflibercept (rch), (“AU Eylea® Label”)
1010	U.S. Publication No. 2015/0071920 A1 (Larson)

Exhibit	Description
1011	U.S. Publication No. 2017/0232199 A1 (Fiedler)
1013	PTE Application U.S. Patent No. 7,374,758, (App. No. 11/016,503)
1014	Robert L. Avery, MD et al., <i>INTRAVITREAL INJECTION TECHNIQUE AND MONITORING Updated Guidelines of an Expert Panel</i> , Retina, J. Retinal and Vitreous Diseases, 34, S1-S18 (2014).
1015	Sahar Awwad et al., <i>Principles of Pharmacology in the Eye</i> , 174 Brit. J. Pharmacol. 4205 (2017).
1016	David M. Brown et al., <i>Intravitreal Aflibercept for Diabetic Macular Edema</i> , 122 American Acad. of Ophthalmology 2044 (2015).
1017	CATT Research Group, <i>Ranibizumab and bevacizumab for Neovascular Age-Related Macular Degeneration</i> , 364 NEJM 1897 (2011).
1018	Nil Celik et al., <i>Intraocular Pharmacokinetics of Aflibercept and Vascular Endothelial Growth Factor-A</i> , 56 Investigative Ophthalmology & Visual Science 5574 (2015).
1019	Steven R. Cohen & Thomas W. Gardner, <i>Diabetic Retinopathy and Diabetic Macular Edema</i> , 55 Dev. Ophthalmol. 137 (2016).
1020	Arup Das, Paul G. McGuire & Sampathkumar Rangasamy, <i>Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets</i> , Ophthalmology (2015).
1022	Elia J. Duh, Jennifer K. Sun & Alan W. Stitt, <i>Diabetic retinopathy: current understanding, mechanisms, and treatment strategies</i> , JCI Insight (2017).
1023	Elwes et al., <i>Clinical Outcomes of Switching to Aflibercept Using a pro re nata Treatment Regimen in Patients with Neovascular Age-Related Macular Degeneration Who Incompletely Responded to Ranibizumab</i> , 18 BMC Ophthalmology (2018).
1024	K Ghasemi Falavarjani & QD Nguyen, <i>Adverse Events and Complications Associated with Intravitreal Injection of Anti-VEGF Agents: a Review of Literature</i> , Eye (2013).

Exhibit	Description
1026	Allen C. Ho et al. <i>Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration</i> , 121 <i>Ophthalmology</i> 2181 (2014).
1029	Su-Eon Jin & Sung-Joo Hwang, <i>Ocular Delivery Systems for the Administration of Antibody Therapeutics</i> , J. Pharm. 47 <i>Investig.</i> 373 (2017).
1030	Lehman Brothers Presentation, 9 th Annual Global Healthcare Conference, Mar. 2006
1031	Joan W. Miller, Saghar Bagheri & Demetrios GF Vavvas, <i>Advances in Age-related Macular Degeneration Understanding and Therapy</i> , 10 <i>U.S. Ophthalmic Rev.</i> 119 (2017).
1034	Quan Dong Nguyen, et al., <i>A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration</i> , 116 <i>Ophthalmology</i> 2141 (2009).
1035	Quan Dong Nguyen, et al., <i>Evaluation of Very High- and Very Low-Dose Intravitreal Aflibercept in Patients with Neovascular Age-Related Macular Degeneration</i> , 28 <i>J. Ocular Pharmacology and Therapeutics</i> 581 (2012).
1037	Lorena Perez-Gutierrez & Napoleone Ferrara, <i>Biology and Therapeutic Targeting of Vascular Endothelial Growth Factor A</i> , <i>Nature Reviews Molecular Cell Biology</i> (2023).
1039	Michael W. Stewart, <i>Clinical and Differential Utility of VEGF Inhibitors in Wet Age-Related Macular Degeneration: Focus on Aflibercept</i> , 6 <i>Clin. Ophthalmol.</i> 1175 (2012).
1041	George Trichonas and Peter K. Kaiser, <i>Aflibercept for the Treatment of Age-Related Macular Degeneration</i> , 2 <i>Ophthalmol. Ther.</i> 89 (2013).
1042	Rohit Varma, et al., <i>Prevalence of and Risk Factors for Diabetic Macular Edema in the United States</i> , 132 <i>JAMA Ophthalmol.</i> 1334 (2014).
1048	Macugen® 2011 Label
1049	Beovu® 2019 Label
1050	Eylea® 2011 Label
1051	Eylea® 2012 Label

Exhibit	Description
1052	Eylea® 2014 Label
1053	Eylea® 2016 Label
1054	Eylea® HD 2024 Label
1055	Lucentis® 2017 Label
1057	Vabysmo® 2022 Label
1058	Assessment Report, Eylea aflibercept, Committee for Medicinal Products for Human Use (CHMP), <i>European Medicines Agency Science Medicines Health</i> , Sept. 2012
1059	Center for Drug Evaluation and Research, “Pharmacology Review(s)” App. No. 125387Orig1s000 (2011) (“Eylea Pharmacology Review”)
1060	EMA Annex
1061	Loureiro et al., <i>Intravitreal Injections of Bevacizumab: The Impact of Needle Size in Intraocular Pressure and Pain</i> , 11 J. Curr. Glaucoma Pract. 238 (2017).
1062	Napoleone Ferrara, <i>Vascular endothelial growth factor and age-related macular degeneration: from basic science to therapy</i> , Nature Medicine (2010).
1063	Roomasa Channa, Michael Smith & Peter A Campochiaro, <i>Treatment of macular edema due to retinal vein occlusions</i> , Clinical Ophthalmology (2011).
1064	William Rhoades et al., <i>Management of macular edema due to central retinal vein occlusion – The role of aflibercept</i> , Taiwan J Ophthalmol. (2017).

IV. SUMMARY OF OPINIONS

13. I provide my opinions from the perspective of a person of ordinary skill in the art (POSA).

14. GROUND 1: It is my opinion that a POSA would have been motivated to combine Vitti, the AU Eylea® Label, and Larson with a reasonable

expectation of success. It is further my opinion that these references teach, or at least make obvious, the methods recited in Claims 1, 4-38 of the '036 patent.

15. GROUND 2: It is my opinion that a POSA would have been motivated to combine Regeneron's Prior Disclosures (Furfine, Dix, and the AU Eylea® Label), Fiedler, and Larson with a reasonable expectation of success. It is further my opinion that these references teach, or at least make obvious, the methods recited in Claims 1, 4-38 of the '036 patent.

16. GROUND 4: It is my opinion that a POSA would have been motivated to combine Vitti, the AU Eylea® Label, and Larson with the 2011 Eylea® Clinical Review. It is further my opinion that these references teach, or at least make obvious, the methods recited in Claims 2 and 3 of the '036 patent.

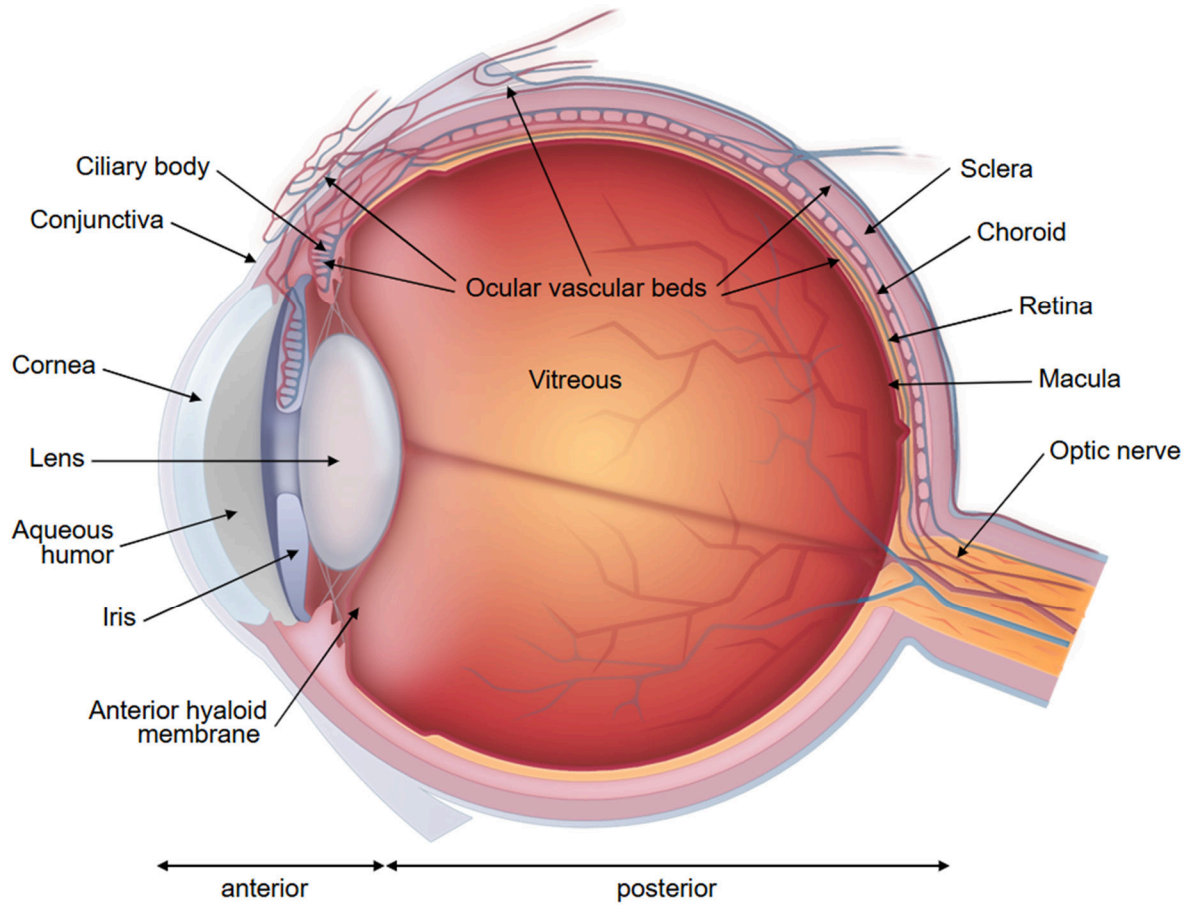
17. GROUND 5: It is my opinion that a POSA would have been motivated to combine Regeneron's Prior Disclosures (Furfine, Dix, and the AU Eylea® Label), Fiedler, and Larson with the 2011 Eylea® Clinical Review. It is further my opinion that these references teach, or at least make obvious, the methods recited in Claims 2 and 3 of the '036 patent.

V. TECHNICAL BACKGROUND

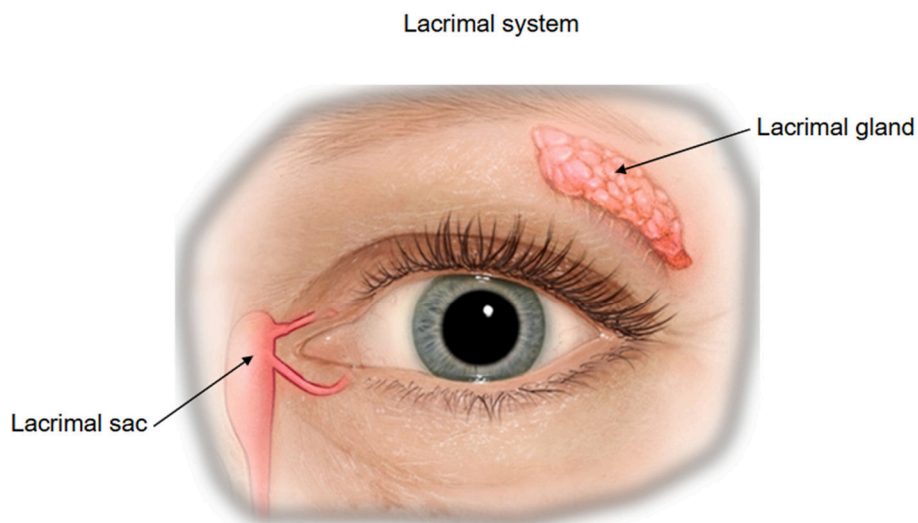
A. Structure of the Eye & Implications for Treatment

18. The eye is a highly specialized organ that allows light to be focused and processed into nerve impulses for interpretation by the brain. EX1015 at 4206. The eye is broadly divided into two compartments called the anterior segment (front of the eye) and posterior segment (back of the eye). EX1015 at 4206; EX1029 at 376. The anterior segment comprises the cornea, conjunctiva, ciliary body, iris, aqueous humor, lens, and lachrymal system. EX1029 at 376. The posterior segment of the eye refers to the posterior two-thirds of the eye, including the anterior hyaloid membrane and all the structures behind it such as the macula, vitreous, retina, choroid, and optic nerve. EX1015 at 4211; EX1029 at 376 (“The posterior segment consists of the retina, vitreous humor, sclera, and choroid.”).

19. A diagram showing the basic anatomy of the eye is below:



20. Further, a diagram showing the basic structure of the lachrymal system is below:



21. The complexities of the eye's anatomy have historically posed challenges to the administration of drugs for treating ophthalmic diseases. For example, physical and biochemical barriers that serve as protection against pathogen entry into the eye also tend to restrict drug permeation. EX1015 at 4205, 4207; EX1029 at 376 (“The main structural barriers for drug application to the eye are (1) the cornea and anterior barriers, (2) the sclera and choriocapillaris, and (3) the retina and blood-retinal barrier”). The least invasive routes for ocular drug administration are topical (e.g., eye drops) and oral (e.g., tablets) formulation. EX1015 at 4207.

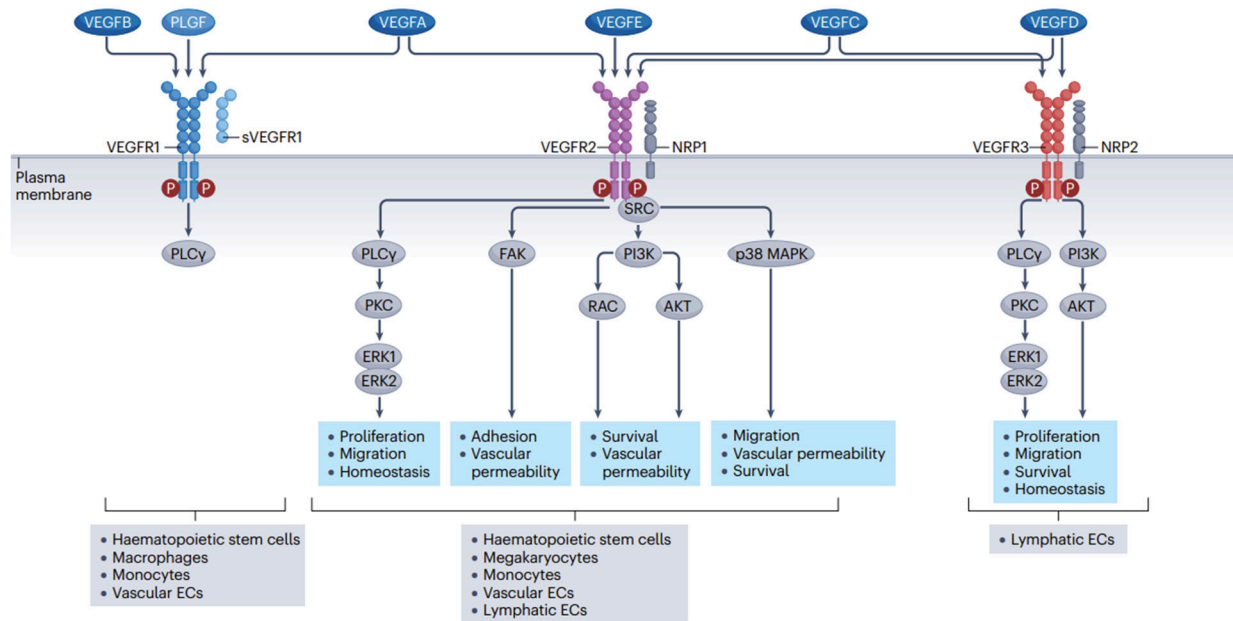
22. The route of administration for treating an eye disease often depends on which segment of the eye is diseased. For anterior segment diseases, the main modality of treatment is local administration (usually eye drops). EX1015 at 4207. Drug delivery to treat posterior segment diseases poses different challenges, often due to the blood-retinal barrier. EX1015 at 4207. The blood-retinal barrier controls fluid and molecular movement between the ocular vascular beds and prevents leakage of macromolecules and harmful molecules into the retina. EX1015 at 4207. As a result, the blood-retinal barrier limits the influx of a drug into the retina and vitreous regions, requiring the systemic administration of high doses to achieve therapeutic concentrations within the eye. EX1015 at 4207. This systemic administration of high doses causes unwanted side effects. EX1015 at 4207. Therefore, intravitreal injections—which I discuss further below—are required to administer drugs directly to the posterior segment to achieve reproducible and high doses. EX1015 at 4207.

B. Vascular Endothelial Growth Factor (VEGF)

23. Blood vessels and blood circulation are critical for bringing nourishment to limbs and organs, such as the eye. Vascular endothelial growth factor (“VEGF”) plays a key role in the formulation of new blood vessels, called

angiogenesis. EX1037 at 1. VEGF is also known as VEGF A following the discovery of several other members of the same gene family (isoforms): VEGFB, VEGFC, VEGFD and placental growth factor. EX1062 (Ferrara 2010) at xx; EX1037 at 1.

24. The VEGF family of ligands binds in a partially overlapping pattern to three receptor tyrosine kinases (RTKs: VEGFR1, VEGFR2 and VEGFR3) as well as two co-receptors (neuropilin1 and neuropilin2). EX1037 at 6. VEGFs bind to the VEGFRs and co-receptors on the cell surface and stimulate cellular responses through receptor dimerization and transphosphorylation as shown in the figure below. EX1037 at 6.



25. The role of VEGF in the normal development of the eye vasculature is well established. EX1037 at 11. The amount of VEGF in the eye is an important factor in process by which certain diseases of the eye develop. EX1037 at 10. If VEGF is overexpressed, it can lead to the development of abnormal blood vessels in the retina. EX1037 at 10. Persistent and unresolved angiogenic cascade—meaning, the process of forming new blood vessels from pre-existing ones—that leads to the formation of leaky or abnormal blood vessels can lead to angiogenic eye disorders. EX1037 at 10.

C. Angiogenic Eye Disorders

26. Angiogenic eye disorders is a term used in the field of ophthalmology to describe a broad class of vascular eye diseases. Angiogenic eye disorders include, but are not limited to, age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, retinopathy of prematurity, optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus,

pterygium, vascular retinopathy, various states of diabetic retinopathy (including non-proliferative diabetic retinopathy and/or proliferative diabetic retinopathy, with or without DME). Below I discuss in further detail several representative angiogenic eye disorders.

1. Age-related macular degeneration (AMD)

27. As of 2017, age-related macular degeneration (AMD) was the third leading cause of blindness worldwide and the leading cause of vision loss in the Western world. EX1031 at 119. Its prevalence is expected to increase because of an aging population, such that it is estimated that close to 288 million people will be affected by AMD by 2040. EX1031 at 119.

28. AMD results from the aging eye's inability to metabolize and dispose completely of photoreceptor outer segments and other waste products. EX1039 at 1. As a result, lipids, particularly, apolipoproteins, accumulate within the innermost layer of the choroid of the eye (also known as Bruch's membrane), leading to chronic ischemia and inflammation. EX1039 at 1.

29. There are two forms of AMD: the non-neovascular or dry form ("dry AMD"), which is the most common, and the neovascular or wet form ("wet AMD"). EX1041 at 90.

30. Wet AMD is responsible for most severe vision loss. EX1041 at 90. Choroidal neovascularization (CNV), which involves the growth of new, abnormal blood vessels in the choroid, is the hallmark of wet AMD. EX1041 at 90; EX1029 at 376 (“Wet AMD is characterized by neovascularization of Bruch’s membrane, which is the innermost layer of the choroid.”); EX1037 at 10. When a person has wet AMD, VEGF is upregulated, leading to the development of pathological retinal neovascularization in the fenestrated endothelium of the choroid. EX1039 at 1; EX1037 at 10; EX1029 at 376. In other words, the upregulation of VEGF causes the growth of new, abnormal blood vessels, which can lead to blindness.

2. Diabetic retinopathy (DR)

31. As of 2014, diabetes mellitus was a disease affecting approximately 347 million persons. EX1042 at 1334. Diabetic eye disease is a leading cause of vision loss in persons aged 20 to 74 years. EX1042 at 1334.

32. Diabetic retinopathy (DR) results from chronic damage to the neurovascular structures of the retina. EX1019 at 1. Diabetic retinopathy is diagnosed clinically based on visible hemorrhages, microaneurysms, cotton wool spots, lipid exudates, and neovascularization. EX1019 at 5. The symptoms of

diabetic retinopathy very widely and may be out of proportion to the severity of retinal pathology. EX1019 at 1.

33. Diabetic retinopathy may be either nonproliferative or proliferative. EX1022 at 1. Non-proliferative diabetic retinopathy (NPDR) is based on clinical findings manifested by visible features, including microaneurysms, retinal hemorrhages, intraretinal microvascular abnormalities (IRMA), and venous caliber changes. EX1022 at 1. Meanwhile, proliferative diabetic retinopathy (PDR) is characterized by pathologic preretinal neovascularization. EX1022 at 1.

3. Diabetic macular edema (DME)

34. Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that occurs across all severity levels of diabetic retinopathy and represents the most common cause of vision loss in patients with diabetic retinopathy. EX1022 at 1; EX1020 at 1375. As of 2016, approximately 500,000 persons in the United States had clinically significant DME. EX1019 at 1.

35. DME is characterized by pericyte loss and endothelial cell-cell junction breakdown that alters the blood-retinal barrier (BRB). EX1020 at 1375. The blood-retinal barrier regulates the fluid electrolyte balance in the retina. EX1020 at 1375. The below figure illustrates three important alterations of the

blood-retinal barrier that occur in diabetes: breakdown of cell-cell junctions formed by endothelial cells; loss of pericyte cells which regulate retinal capillary blood flow; and thickening of the basement membrane which provides structural support, acts filtration barrier, and regulates cell proliferation and differentiation. EX1020 at 1378-1379.

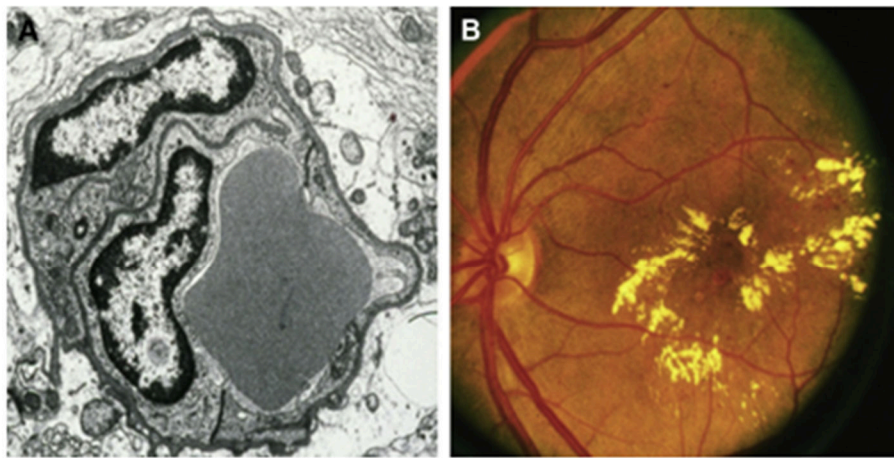


Figure 2. Blood–retinal barrier alteration in diabetes. **A,** Electron microscopic view of a monkey retinal capillary showing endothelial cells joined by tight junctions and surrounded by pericytes and a thin basement membrane between cells. **B,** Fundus photograph of a diabetic patient showing microaneurysms, retinal hemorrhages, and hard exudates in the macula. There is also exudation of plasma in the macula, leading to clinically significant macular edema.

4. Macular Edema Following Retinal Vein Occlusion

36. Retinal vein occlusion (RVO) is a prevalent retinal vascular disease, second only to diabetic retinopathy. EX1063 at 705 at 705. As of 2011, the incidence of RVOs is estimated to be 180,000 per year in the US. EX1063 at 705.

37. There are two types of retinal vein occlusions (RVO), central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). EX1063 at

705. In CRVO, there is obstruction of the major outflow channel of the eye, resulting in effects throughout the entire retina, including hemorrhages; cotton wool patches, which represent nerve layer infarcts; edema; and capillary occlusion. EX1063 at 705. In BRVO, a tributary of the central retinal vein is obstructed and only the portion of the retina that is drained by the tributary is affected. EX1063 at 705. The consequences of BRVO are similar to those seen in CRVO (hemorrhages, cotton wool patches, edema, capillary occlusion), but tend to be less severe because a portion of the retina has normal venous drainage. EX1063 at 705.

38. The obstruction in venous outflow after CRVO or BRVO increases intraluminal venous pressure and causes transudation of plasma and blood, resulting in edema and hemorrhages throughout all or most of the retina for CRVO and throughout the drainage area of a BRVO. EX1063 at 706. Ultimately, CRVO can cause vision loss. EX1064 at 70. Vision loss due to CRVO is commonly caused by macular edema. EX1064 at 70. As of 2016, the most common therapy used to treat macular edema due to central retinal vein occlusion was intravitreal inhibition of VEGF including through intravitreal injection of aflibercept. EX1064 at 70, 72.

D. Treatment of Angiogenic Eye Disorders with Anti-VEGF

39. Anti-VEGF drugs have revolutionized the treatment of neovascular eye disorders such as age-related macular degeneration. EX1037 at 1. As of May 2018, the FDA has approved numerous anti-angiogenic drugs for the treatment of intraocular neovascular disorders including aflibercept, ranibizumab, pegaptanib, and bevacizumab (used off label). EX1037 at 12.

40. These anti-VEGF drugs fall into one of two categories: monoclonal antibodies or fusion proteins. EX1041 at 90. Anti-VEGF monoclonal antibodies act via direct interaction with binding domains on either soluble VEGF ligands or membrane-bound receptors, as discussed above in Section V.B. EX1041 at 91. In contrast, fusion proteins act as decoy receptors, binding with high affinity to the VEGF-A ligand; thus, preventing binding and subsequent activation of VEGF receptor (VEGFR) 1 and VEGFR2. EX1041 at 91.

1. Aflibercept (Eylea®, Eylea HD®)

a. Identification and Mechanism of Action

41. Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. EX1053 at Section 11; EX1041 at 89, 91. Aflibercept acts as a soluble decoy

receptor that binds VEGF-A and PlGF and thereby can inhibit the binding and activation of these cognate VEGF receptors. EX1053 at Section 12.1. This process is also referred to as acting as a “VEGF-trap.” Aflibercept exhibits higher affinity for VEGF-A/-B and binds all the VEGF isoforms (VEGF-B and -C, placental growth factor). EX1041 at 89.

42. For the treatment of ophthalmic diseases, aflibercept is administered intravitreally to exert local effects in the eye. EX1053 at Section 12.3. In patients with wet AMD, RVO, DME, or DR with DME following intravitreal administration of Eylea®, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept:VEGF complex. EX1053 at Section 12.3. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept:VEGF complex). EX1053 at Section 12.3.

b. Clinical Trials

43. Regeneron conducted a series of clinical trials supporting the safety and efficacy of aflibercept. As it relates to the issues I have been asked to opine on, these clinical trials demonstrate that increasing the dose of aflibercept would

prolong its duration of action in the eye resulting in a reduction of the frequency of injections for patients. EX1039 at 1182. The clinical trials also supported that there was no likely risk of drug toxicity with increasing the dose of aflibercept to 8 mg. EX1058 at 20-21. I discuss relevant clinical trials below.

44. The Phase I CLEAR-IT 1 (Clinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial) investigation was designed to “determine the safety, tolerability, maximum tolerated dose, and bioactivity” of intravitreally administered aflibercept in patients with nAMD. EX1034 at 2141; EX1039 at 1180; EX1041 at 92. The CLEAR IT study found that single doses of aflibercept between 0.05 mg and 4 mg were tolerated well by 21 patients. EX1034 at 2141; EX1039 at 1180. Of six patients followed for 12 weeks, three did not require additional injections. EX1034 at 2147; EX1039 at 1180.

45. Based on the results of CLEAR-IT 1, the developers hoped to show that aflibercept could be dosed less often than monthly. EX1039 at 1180. The Phase II CLEAR-IT 2 trial randomized 159 patients to receive three injections of 0.5 mg or 2 mg, or single doses of 0.5 mg, 2 mg, or 4 mg, with final evaluations at 12 weeks. EX1039 at 1180. Visual improvement at week 8 was similar in patients receiving single doses or three doses. EX1039 at 1180. During the second phase

of the CLEAR-IT 2 study, patients were followed from week 16 through 52 and given injections as needed. EX1039 at 1180. An average of two injections was required, with a mean time to first injection of 129 days. EX1039 at 1180. The Phase II CLEAR-IT 2 investigation demonstrated that “patients treated as needed required few injections, yet maintained excellent gains in vision.” EX1039 at 1180. Patients receiving three monthly “loading” doses achieved superior visual results compared with those receiving single injections. EX1039 at 1180.

46. The concurrent Phase III VIEW (Vascular Endothelial Growth Factor [VEGF] Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration Studies) 1 and VIEW 2 trials of aflibercept compared the results of ranibizumab 0.5 mg, aflibercept 0.5 mg, aflibercept 2 mg every 4 weeks, or aflibercept 2 mg every 8 weeks after three monthly loading doses. EX1039 at 1181. Patients in the VIEW studies were randomized 1:1:1:1 to receive ranibizumab 0.5 mg, aflibercept 0.5 mg, aflibercept 2 mg every 4 weeks, or aflibercept 2 mg every 8 weeks after three monthly loading doses. EX1039 at 1181. All aflibercept arms in both trials achieved the primary endpoint, i.e. noninferiority compared with ranibizumab for maintenance of vision. EX1039 at 1181. Both aflibercept and ranibizumab were well tolerated by patients in both

VIEW trials. EX1039 at 1181. There were no significant differences between aflibercept and ranibizumab in the incidences of serious ocular adverse events (1.6% and 2.3% versus 3.0% and 3.1%, respectively) or systemic side effects (1.6% and 1.9% versus 1.7% and 1.7%). Based on the one-year efficacy and safety results of the VIEW trials, the FDA approved the 2 mg dose of aflibercept for the treatment of exudative AMD. EX1039 at 1181. The recommended treatment regimen includes three loading injections at 4-week intervals, followed by injections every 8 weeks. EX1039 at 1181.

47. During year 2 of the VIEW trials, patients continued receiving the same drug and dose as in year 1, were evaluated every 4 weeks, and were given injections as needed, but at intervals not exceeding 12 weeks. EX1039 at 1181. Fewer patients receiving aflibercept required the most intensive treatments; 15.9% of patients initially receiving aflibercept and 26.5% of patients initially receiving ranibizumab required at least six injections, and 1.9% and 3.1% required at least 11 injections. EX1039 at 1181. Patients receiving aflibercept 2 mg required an average of 4.2 injections, whereas patients receiving ranibizumab required an average of 4.7 injections. EX1039 at 1181.

48. The VIEW trials showed that aflibercept 2 mg every 8 weeks produced vision gains comparable with aflibercept 0.5 mg every 4 weeks (+7.9 and +8.9 letters versus +6.9 and +9.7 letters). EX1039 at 1182. Thus, the results of the VIEW 1 and VIEW 2 studies suggest “that increasing the dose of a drug prolongs its duration of action (durability).” EX1039 at 1182.

49. As reported in Brown *et al.* 2015, Regeneron studied for 100 weeks the efficacy and safety of two dosing regimens of intravitreal administered aflibercept as compared with macular laser photocoagulation for diabetic macular edema (DME) in the phase III VISTA^{DME} and VIVID^{DME} studies. EX1016 at 2044. Brown discusses that “[d]iabetic retinopathy is the most common microvascular complication of diabetes mellitus and the leading cause of blindness in working-age adults in the United States, Europe, and increasingly worldwide.” EX1016 at 2044. DME is a manifestation of DR and “is a major cause of the vision loss associated with diabetic retinopathy.” EX1016 at 2044. Patients in the VISTA^{DME} and VIVID^{DME} trials had one eye per patient enrolled in the study. EX1016 at 2044. Eyes were randomized in a 1:1:1 ratio to receive 2 mg aflibercept every 4 weeks, 2 mg aflibercept every 8 weeks after five initial monthly

doses, or macular laser photocoagulation. EX1016 at 2045. Eyes were treated for 96 weeks. EX1016 at 2044.

50. Brown reported that after 100 weeks, both the VISTA^{DME} and VIVID^{DME} trials showed “a significantly greater proportion of eyes treated with IAI [i.e., intravitreal aflibercept] experienced an improvement of ≥ 2 steps in the DRSS score compared with eyes treated with laser control, suggesting that IAI also may promote regression of the underlying diabetic retinopathy in addition to the treatment of DME.” EX1016 at 2044.

c. Aflibercept Toxicity Data

51. The toxicity of VEGF Trap was evaluated in both single-dose and repeat-dose preclinical toxicity studies. EX1058 at 19-22.

52. One such single-dose study, VGFT-TX-06008 “AVE0005 [VEGF Trap]: Exploratory Single-Dose Intravenous (30-Minute Infusion) Toxicity Study in Rats with 2-Week Observation Period,” was described in the Pharmacology Review submitted to the FDA during the regulatory approval process.). EX1059 at 20. A single 30-min intravenous (IV) infusion of VEGF Trap was given to rats at doses of 50, 150, and 500 mg/kg. EX1059 at 20; EX1058 at 19. Researchers observed lesions at the injection site within the 50 mg/kg and 500 mg/kg groups

and moderate dose-related decrease in mean body weight gain in males at all doses. EX1059 at 20; EX1058 at 19. The researchers concluded that the No Observed Adverse Effect Level (“NOAEL”) was 150 mg/kg since, at this dose level, “the effect on weight gain reversed by the end of the study;” however, the reviewing pharmacologist considered that a NOAEL cannot be identified in the males due to the significant decrease in body weight gain and that only the NOAEL in the female group was greater than 500 mg/kg. EX1059 at 20; EX1058 at 19.

53. A similar study, VGFT-TX-06007 “AVE0005 [VEGF Trap]: Exploratory Single-Dose Intravenous (30-Minute Infusion) Toxicity Study in Rats with 2-Week Observation Period,” was described in a Summary Report submitted during the regulatory approval process. EX1059 at 11, 20. A single IV infusion of VEGF Trap was given to rats at doses of 150 and 500 mg/kg. EX1059 at 11, 20. Researchers noted skin lesions in both dose groups. Further, researchers observed a moderate decrease in body weight gain in both dose groups across both sexes, discoloration of the tail in the 150 mg/kg group, and decreased food intake in females at 500 mg/kg. EX1059 at 20; EX1058 at 19. Researchers also found that

the maximum tolerated dose was greater than 500 mg/kg. EX1059 at 20; EX1058 at 19.

54. Several repeat-dose toxicity studies were conducted in Cynomolgus monkeys using intravitreal (IVT) administration. EX1058 at 20-21. Regeneron conducted additional repeat-dose toxicity studies in mice, rats, and Cynomolgus monkeys where VEGF Trap was delivered via IV injection and subcutaneous (SC) injection. EX1058 at 20-21.

55. Two such groups of IVT studies, sub-chronic studies (up to 13 weeks) and chronic studies (up to 8 months) were performed on monkeys. EX1058 at 20. Researchers observed an inflammatory response in the anterior chamber that occurred in eyes treated with VEGF Trap (not dose or treatment-related) which “peaked at 2 days and resolved within 3 weeks.” EX1058 at 20. Researchers noticed ocular pressure in the VEGF Trap and placebo groups due to the increase in vitreal volume following injection of 50 microliters per eye. EX1058 at 20. This was supported by the observation that administration of a lower volume of 25 microliters would cause a smaller post-dose increase in ocular pressure which was reversible. EX1058 at 20. Researchers examined monkeys for retinal damage

using angiography or electroretinography and did not find any damage. EX1058 at 20.

56. Specifically, within the 8-month repeat dose toxicity study in monkeys, researchers saw “increased incidence of epithelial erosion/ulceration of the respiratory epithelium of the nasal turbinates, often accompanied by chronic-active inflammation of the nasal turbinates at a dose of 2000 micrograms per eye.” EX1058 at 20. Researchers determined this effect was likely a result of “local exposure of the nasal epithelium to the nasal cavity by way of anastomoses between the ophthalmic and nasal venous plexuses, or leakage from the IVT injection site into the nasal lacrimal duct.” EX1058 at 20. Researchers established a NOAEL of 500 microgram per eye based on “findings of epithelial erosion/ulceration or nasal turbinates noted at the 2 and 4 mg/eye levels.” EX1058 at 20.

57. Although inflammation in the anterior chamber was identified at all dose levels, a tentative NOAEL was proposed because this effect “may be considered mild and reversible.” EX1058 at 20. Researchers compared the drug exposure in monkeys to the clinical exposure and found that animal exposure was 231 times higher, based on total drug exposure over time (“AUC”) and Lowest

Observed Adverse Effect Level (“LOAEL”) values and 708 times higher based on highest concentration (“Cmax”) and LOAEL values. EX1058 at 20.

58. A group of studies was performed to examine systemic toxicity in mice, rats, and monkeys. EX1058 at 20. Researchers could observe systemic toxicities because “exposure to free VEGF Trap was much higher in these studies compared to IVT administration.” EX1058 at 20. Such toxicities included target organs including “bone (interference with growth plate maturation of long bones and osteocartilaginous exostoses of vertebrae), kidney (frequently increased glomerular mesangial matrix, occasionally hyperplasia of parietal epithelium and periglomerular fibrosis), adrenals (decreased vacuolation with eosinophilia in the zona fasciculata), ovary (decreased number of maturing follicles, granulosa cells and/or theca cells), and nasal cavity (respiratory and olfactory epithelium of nasal turbinates).” EX1058 at 20. Similar findings were seen in a 6-month study on monkeys which included “vascular alterations in the choroid plexus (≥ 3 mg/kg) and digestive tract (≥ 10 mg/kg), vascular degeneration and fibrosis in several tissues (≥ 10 mg/kg) including the heart, and hepatic portal inflammation and periportal necrosis (30 mg/kg).” EX1058 at 20. The NOAEL could not be determined because of the effects on target organs and microscopic findings.

Researchers compared the drug exposure in animals to the clinical exposure and found that animal exposure “ranged from 134- to 1546-fold, based on AUC and LOAEL values and 503- to 4902-fold, based on Cmax and LOAEL values. It was “considered that following IVT VEGF Trap administration, levels of free VEGF Trap are unlikely to be seen at levels to cause systemic toxicity.” EX1058 at 20-21.

d. Low Dose (2 mg) Approvals

59. Aflibercept has been approved in the United States and internationally including, for example, in Europe and Australia. EX1009; EX1053. In the U.S., it has been approved by the FDA for treatment of wet AMD, RVO, DME, and DR. EX1053. Initially Eylea® was approved to treat “Neovascular (Wet) Age-Related Macular Degeneration (AMD)” in 2011 with a recommended dose and administration of “2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).” EX1050 at 1. Further, “Macular Edema Following Central Retinal Vein Occlusion (CRVO)” was approved in September 2012 with a recommended dose and administration of “2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks

(monthly).” EX1051 at 1. In 2014, Eylea® was approved to treat “Diabetic Macular Edema (DME)” with a recommended dose and administration of “2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).” EX1052 at 1. Further, the label broadened the approved treatment for CRVO where the indication was expanded to “Macular Edema Following Retinal Vein Occlusion (RVO)” in 2014 with the same recommended dose and administration. EX1052 at 1. The indication was later broadened to include “Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema” with the same recommended dose and administration for each as existed for DME when it was added in 2014. EX1053 at 1.

e. Overdoses

60. During the clinical development for low dose intravitreal Eylea® (2 mg), investigators also administered 4 mg and 8 mg doses. The 8 mg doses were termed “overdoses” and reported by Regeneron (via Regeneron’s ex-US development partner, Bayer) to regulatory agencies in both Australia (Therapeutics Goods administration (TGA) and Europe (European Medicines Agency (EMA))).

EX1009 at 35; EX1060 at Section 4.9 (“In clinical trials, doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred.”). Notably, in clinical trials, Regeneron reported that “doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated.” EX1009 at 35.

61. Clinical trial results referenced in the EMA assessment report also showed that when a patient received a 500 µl, 20 mg dose, the only adverse event identified was a short-term increase in intra ocular pressure (IOP), which is a common adverse event associated with intravitreal injections, particularly with injectate volumes exceeding 0.1 ml. EX1058 at 65. For context, 20 mg is 10x the recommended dose of Eylea® and 500 µl is 5x the recommended maximum volume for intravitreal injection. EX1058 at 64.

62. If an overdose is associated with increased volume, doctors are instructed to monitor pressure, and initiate treatment if necessary. EX1058 at 65 (“Recommended treatment: overdoses of up to 20 mg/eye were generally well tolerated. Overdosing was associated with increased injection volume and subsequently with increased IOP. Therefore, when overdose is associated with increased volume, IOP should be monitored and if deemed necessary by the

treating physician, adequate treatment should be initiated.”); EX1060 at Section 4.9 (“Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated”); EX1009 at 35 (“Overdosing was associated with increased injection volume and subsequently with increased intraocular pressure. Therefore, in case of overdosage intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.”).

63. Likewise, the Eylea HD® Label characterizes overdoses in terms of injection volume: “Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.” EX1054 at Section 10.

f. High Dose (8 mg) Approval

64. Regeneron’s high dose (8 mg) formulation of aflibercept, Eylea HD®, has also been approved in the United States and internationally. EX1054. In the United States, the FDA has approved Eylea HD® for treatment of “Neovascular (Wet) Age-Related Macular Degeneration (nAMD),” “Diabetic Macular Edema

(DME)” and “Diabetic Retinopathy (DR).” EX1054 at 1. For nAMD and DME the recommended administration and dosage is “8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week.” EX1054 at 1. For DR, the recommended administration and dosage is the same except the label specifies “once every 8 to 12 weeks” after the first three doses instead of “once every 8 to 16 weeks” as described in the recommendation for nAMD and DME. EX1054 at 1.

2. Other Anti-VEGF Treatments

a. Pegaptanib (Macugen®)

65. Pegaptanib is a selective VEGF antagonist designed for intraocular use. EX1048 at Section 12.1; EX1020 at 1382. This VEGF antagonist is an aptamer that adopts a three-dimensional conformation which allows it to bind to extracellular VEGF. EX1048 at Section 12.1. “Under in vitro testing conditions, Pegaptanib binds to the major pathological VEGF isoform, extracellular VEGF₁₆₅, thereby inhibiting VEGF₁₆₅ binding to its VEGF receptors.” EX1048 at Section 12.1.

66. Pegaptanib was approved by the FDA for treatment of nAMD.

EX1048 at 1. The label indicates that a 0.3 mg / 90 microliter dose should be administered once every six weeks by intravitreal injection into the eye. EX1048 at 1. Further, administration of pegaptanib is performed using a 30-gauge needle. EX1048 at 2.

b. Ranibizumab (Lucentis.®)

67. Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. EX1037 at 12, 14. Ranibizumab blocks all isoforms of VEGF-A and is “affinity-enhanced” to provide stronger affinity to bind to VEGF-A. EX1020 at 1382. Ranibizumab has been approved by the FDA for treatment of nAMD, DR, DME, RVO, and mCNV. EX1055 at 1. Ranibizumab is intravitreally injected with a 30-gauge x ½ inch needle. EX1055 at Section 2.7. The HARBOR clinical trial for ranibizumab, discussed below at Section V.D.1.b, “showed that patients receiving PRN ranibizumab 0.5 mg required 7.7 injections during the year whereas those receiving PRN ranibizumab 2 mg required an average of 6.9 injections.” EX1039 at 1182.

c. Off-Label Bevacizumab (Avastin®)

68. Bevacizumab is a full-length humanized monoclonal antibody, approximately 3 times the size of the ranibizumab molecule, that also blocks all isoforms of VEGF-A. EX1020 at 1382. Although it only has FDA approval for the treatment of cancer, bevacizumab is widely used off-label for the treatment of wet AMD, diabetic macular oedema, and retinal vein occlusion. EX1037 at 14; EX1020 at 1382. Off-label use of bevacizumab is supported by the CATT (Complications of Age-related Macular Degeneration Treatment Trials) investigation, which showed that monthly bevacizumab produced vision gains comparable with monthly ranibizumab.” EX1039 at 1182. Like ranibizumab, bevacizumab has been intravitreally injected off label at 50 microliters with a 30-gauge needle. EX1017 at 1898; EX1061 at 38.

d. Other VEGF Antagonists

69. Other anti-VEGF antagonists that have been approved by the FDA as therapeutics for multiple intraocular neovascular disorders include brolucizumab, a single-chain variable fragment that targets VEGFA, and faricimab, a bispecific antibody that targets VEGFA and angiopoietin. EX1049 at 1; EX1057; EX1037 at 14. Brolucizumab is administered as a 6 mg dose (120 mg/ml) in a 50-microliter

intravitreal injection. EX1049 at 1. Faricimab is administered as a 6 mg dose (120 mg/ml) in a 50 microliter intravitreal injection. EX1057 at 1.

E. Intravitreal Injections

70. Intravitreal injections, or injections into the eye have been performed in ophthalmology for more than 100 years. At its most basic level, intravitreal injection involves the administration of drug through a small needle inserted directly into the eye. Intravitreal injection of anti-VEGF drugs revolutionized the treatment of common angiogenic eye disorders, including for example diabetic retinopathy (DR), age-related macular degeneration (AMD), and retinal vein occlusion. EX1024 at 787. The use of intravitreal injections, however, is not without limits, risks, and burdens to patients which I discussed in turn below.

1. Limits on intravitreal injection volume

71. As I discuss above, the eye is a highly specialized and sensitive organ in the human body. EX1015 at 4206. Intravitreal injection of anti-VEGF therapies can temporarily increase the interocular pressure (IOP) in the eye. EX1014 at S14. The increase in IOP may impair vision. Physicians providing intravitreal injections monitor IOP post-injection to ensure there is no sustained increased IOP,

which can require further intervention to avoid further damage to the eye. EX1014 at S14.

72. It has been well understood in the field for well over a decade that due to the risk of increased IOP with intravitreal injections, there are limits to the volume of an anti-VEGF drug that can be injected into the eye. Typically, as reported in the literature, “[t]he normal volume of intravitreal injection that does not affect vision is in the range of 20-100 μ L.” EX1029 at 377. As my colleagues and I reported as part of an expert panel on updated guidelines for intravitreal injections technique and monitoring, “[i]njection volumes in excess of 0.1 mL can produce dramatic increases in IOP.” EX1014 at S11. The injection volume chart below describes the injection volumes for anti-VEGF intravitreal injections.

Drug Name	Brand Name	Dose	Injection Volume	Indication	Source
Pegaptanib	Macugen®	3 mg	0.09 mL	nAMD	EX1048 at 1
Ranibizumab	Lucentis®	0.5 mg	0.05 mL	nAMD, RVO, mCNV	EX1055 at 1
Ranibizumab	Lucentis®	0.3 mg	0.05 mL	DME, DR	EX1055 at 1
Bevacizumab	Avastin®	1.25 mg	0.05 mL	Off-label use: nAMD, DME, DR, RVO	EX1017 at 1898
Aflibercept	Eylea®	2 mg	0.05 mL	nAMD, RVO, DME, DR	EX1053 at 1

Drug Name	Brand Name	Dose	Injection Volume	Indication	Source
Brolucizumab	Beovu®	6 mg	0.05 mL	nAMD	EX1049 at 1
Faricimab	Vabysmo®	6 mg	0.05 mL	nAMD, DME	EX1057 at 1

2. Adverse events

73. While effective in delivering therapeutic drugs to the posterior segment of the eye, intravitreal injections have potential risks for patients. EX1053 at Sections 5 (Warnings and Precautions), 6 (Adverse Reactions). As discussed, increased IOP is a common adverse event associated with intravitreal injections. EX1053 at Section 5.2 (“Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA®.”). There are others. EX1053 at Sections 5 (Warnings and Precautions), 6 (Adverse Reactions). For example, adverse events associated with intravitreal injections include physical trauma to the eye such as bleeding or retinal detachment, infection which is termed endophthalmitis, or intraocular inflammation (pseudo-endophthalmitis) caused by penetration of the retina by the needle. EX1024 at 788-790; EX1015 at 4207.

3. Treatment burden

74. In addition to the possibility of adverse events as described above, patients receiving long-term, frequent intravitreal injections face considerable logistical, emotional, and financial burdens. EX1047 at S3.

75. Many patients express fears of having injections in the eye, anticipating pain or discomfort. EX1047 at S8. Further, due to age-related challenges, many patients also have difficulty arranging and travelling to appointments for treatment and monitoring. EX1047 at S8. This is unsurprising given that “[i]n a survey of 75 patients with nAMD (mean age=79 years), the reported mean time per visit was 11.7 hours, accounting for appointment preparation, travel, waiting time, treatment time, and post-appointment recovery.” EX1047 at S8. In that same study, “[m]ost patients (72%) reported that they were driven to their appointments by a caregiver, requiring a significant amount of caregiver time away from work or personal activities.” EX1047 at S8.

76. Moreover, treatment and follow-up monitoring of patients receiving long-term, frequent intravitreal injections scan also pose considerable burden on physicians and their clinical staff. EX1047 at S8. In one survey, “67% of the

physicians indicated that it would be very desirable to reduce the number of office visits for the treatment and monitoring of patients with nAMD.” EX1047 at S8.

F. Optimizing Anti-VEGF Therapeutic Strategies

77. Most intravitreal injection treatments require repeat injections to maintain therapeutic effect over time. EX1015 at 4212; EX1018 at 5576 (“For the treatment of nAMD anti-VEGF medications have often to be injected monthly and over a long period of time.”). With each injection, there is a “small but significant risk of blinding complication” and “frequent (4-8 weeks) anti-VEGF treatment will result in a cumulative increase.” EX1015 at 4212. “Less injections are desirable because of patient’s discomfort and injection-related risks like endophthalmitis.” EX1018 at 5576.

78. As of 2017, “[d]ue to the invasive nature and the associated risks of [intravitreal] injections there is much effort to develop longer lasting therapies, which require a reduced dosing frequency.” EX1015 at 4213.

79. As of February 2018, “[t]o address [] challenges [faced by patients receiving long-term, frequent intravitreal injections] and reduce the number of yearly injections, studies have examined alternative dosing regimens, including

extended fixed intervals, as needed, and treat-and-extend strategies in specific nAMD patient populations.” EX1047 at S3.

80. As of 2023, there remained “a need to develop agents with longer-lasting therapeutic effects after intraocular injection, with a number of approaches to this end having been attempted.” EX1037 at 14.

1. Alternative Dosing Strategies

81. To reduce the number of patient visits and injections, clinicians have explored alternative dosing strategies including extended dose intervals, treat-and-extend, pro re nata (PRN) dosing, and interleaving a second anti-VEGF agent at shorter intervals than suggested for a single agent.

82. For example, studies have investigated the effects of quarterly fixed-interval intravitreal injections. EX1047 at S8. These studies showed that quarterly fixed-interval dosing is not sufficient to maintain the initially gained best corrected visual acuity from the monthly treatment. EX1047 at S8.

83. Another approach to decrease the number of intravitreal injections has been to employ a “treat-and-observe (PRN) or treat-and-extend regimen” rather than to follow protocol-driven therapy. EX1039 at 1183; EX1023 at 1. The CLEAR-IT 2 study demonstrated that patients treated as needed with aflibercept

required fewer injections yet maintained excellent gains in vision. EX1039 at 1180. And “many retina specialists in clinical practice individualize treatment regimens in an effort to reduce patient burden. Viable dosing regimens, such as treat-and-extend and pro re nata (PRN; as needed) administration, are used frequently and may reduce treatment burden.” EX1026 at 2182.

2. Increasing dosage

84. To address patient concerns with frequent, uncomfortable injections into the eye, as well as the cumulative incidence of ocular complications, the field began to investigate ways to reduce the frequency of administration by increasing the duration of action through increasing dosage. EX1039 at 1183 (studies showed that decreases the number of intravitreal injections decreases the cumulative incidence of ocular complications for a patient). Even before clinical investigation, “previously published models [] predict[ed] that increasing the dose of an effective anti-VEGF drug has a greater effect on its durability than its efficacy.” EX1039 at 1183. Those predictions proved correct as shown by multiple clinical trials.

85. For example, investigators evaluating ranibizumab studied the effects of increasing the dosage for intravitreal administration in the HARBOR clinical trial. EX1026 at 2181. HARBOR was a 24-month, phase III, randomized,

multicenter, double-masked, dose-response study. EX1026 at 2182. The objective of the study was to evaluate the 24-month efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly and on an as-needed (PRN) basis in treatment-naïve patients with subfoveal neovascular age-related macular degeneration (wet AMD). EX1026 at 2182. “These results are consistent with previously published models which predict that increasing the dose of an effective anti-VEGF drug has a greater effect on its durability than its efficacy.” EX1039 at 1183. As part of HARBOR, ocular and systemic safety events also were evaluated through month 24. EX1026 at 2183.

86. The HARBOR investigators concluded that at 12 months, the ranibizumab 2.0 mg monthly administration group did not meet the prespecified superiority comparison and the 0.5 mg and 2.0 mg PRN groups did not meet the prespecified noninferiority (NI) comparison. EX1026 at 2187. The investigators further observed that the PRN groups required approximately four fewer injections than the monthly groups. EX1026 at 2188. Regarding safety, the HARBOR study demonstrated there were no new safety events observed despite a 4-fold dose escalation in the study. EX1026 at 2190.

87. Researchers in the field were similarly looking at the benefits of increasing the dosage of aflibercept. EX1035 at 586. Nguyen 2012 evaluated the safety, tolerability, and bioactivity of high and low doses of aflibercept in a prospective, double-masked, randomized Phase 1 clinical trial known as the CLEAR-IT 1 trial. EX1035 at 586. Patients received single intravitreal injections of 0.15 mg and 4 mg doses of aflibercept in patients with neovascular AMD. EX1035 at 586. After 8 weeks of study, the investigators concluded that “eyes treated with 4 mg intravitreal aflibercept showed no evidence of inflammation and were indistinguishable from eyes injected with 0.15 mg of intravitreal aflibercept with regard to safety and tolerability.” EX1035 at 586. The Nguyen 2012 paper further reported that “[t]he safety and tolerability profiles of both doses were identical during the 8-week study, with AEs generally being mild-to-moderate and self-limited.” EX1035 at 586.

88. The investigators recognized that there remains unmet at the time for enhancing drug activity and optimizing drug delivery. EX1035 at 587. The Nguyen 2012 paper recommends a solution to these problems—“[a]n improvement to the current therapeutic options would be to increase the duration of drug activity, so that intravitreal injections can be administered less frequently.”

EX1035 at 587. Nguyen 2012 further states that the study results “help to provide uncontroversial support for a dose-response effect of intravitreal aflibercept in neovascular AMD” noting equal importance in the “lack of any increase in AEs associated with the higher dose, suggesting that the higher dose of intravitreal aflibercept may have increased bioactivity, but did not carry additional risks of deleterious effects during the 8-week study.” EX1035 at 587. Nguyen 2012 concludes that “[t]he study also provides additional data to support a dose-dependent bioactivity of intravitreal aflibercept.” EX1035 at 587.

VI. LEVEL OF KNOWLEDGE OF ONE OF ORDINARY SKILL IN THE ART PERTAINING TO THE '036 PATENT

89. I have been informed that the claims of a patent are judged from the perspective of a hypothetical “person of ordinary skill in the art” (“POSA”). I also understand that “the art” is the field of technology to which the patent is related. The purpose of a POSA is to provide an objective viewpoint. I understand that the question of validity is viewed from the perspective of a POSA, and not from the perspective of a lay person, an inventor, or a period of extraordinary skill in the art. I have been informed that the claims of the '036 Patent are to be interpreted as a POSA would have understood them at the relevant time, which I have been asked to assume is May 10, 2018

90. A person of ordinary skill in the art (“POSA”) at the time of the invention would have been a multidisciplinary team that included (1) a medical doctor in ophthalmology or a similar field with knowledge of angiogenic eye disorders, including treatments and dosing regimens of drugs for intravitreal injection including anti-VEGF drugs, at least several years conducting research on anti-VEGF treatments for angiogenic eye disorders, and familiarity with the pharmacological properties of anti-VEGF treatments; and (2) a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture, and characterization of therapeutic proteins, including for example, fusion proteins or antibodies. The POSA would have also had access to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs.

91. At the relevant time of the ’036 patent conveyed to me by counsel, May 2018, I was at least a person of ordinary skill in the art by virtue of my clinical background. For example, I have been a board certified ophthalmologist since 1982 and have treated patients with angiogenic eye disorders for over three

decades, including with intravitreal administration of anti-VEGF drugs. I also have spent several years conducting research on anti-VEGF treatments for angiogenic eye disorders, and have familiarity with the pharmacological properties of anti-VEGF treatments, including aflibercept.

VII. THE '036 PATENT

92. I have reviewed the '036 patent and its prosecution history. The '036 patent, titled “Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins,” issued on December 17, 2024. Regeneron is listed as assignee on the front page of the '036 patent. The '036 patent claims priority to provisional application No. 62/669,506 filed on May 10, 2018. Ex. 1001 ('036 patent).

93. I understand from counsel for Alvotech that the claims of the '036 patent define the scope of the legal rights of the patent. There are two independent claims which are claims 1 and 35. Claim 1 recites a method for treating an angiogenic eye disorder as follows:

1. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising:

administering, intravitreally into an eye of the subject, in a volume of about 100 microliters or less, at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component;

wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein and having a viscosity of about 5-15 centiPoise (cP) at 20° C.

Ex. 1001, 61:51-61.

94. Further, claim 35 recites a method for treating an angiogenic eye disorder as follows:

35. A method for treating an angiogenic eye disorder in a human subject in need thereof comprising:

administering, intravitreally into an eye of the subject, about 70 microliters of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C.

Ex. 1001, 64:29-34.

95. The technology described in the '036 patent relates to methods for treating angiogenic eye disorders, e.g., age-related macular degeneration (wet), diabetic macular edema, or diabetic retinopathy, using ophthalmic formulations with high concentrations of VEGF receptor fusion protein. Ex. 1001, Abstract, 2:20-24, 8:22-37.

96. The patent describes angiogenic eye disorders as “any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels and/or by blood vessel leakage.” Ex. 1001, 29:19-22. The patent describes treatment of these disorders using of ophthalmic formulations which generally include five components: VEGF receptor fusion protein (e.g., aflibercept), buffer (e.g., histidine-based, phosphate-based, acetate-based, or citrate-based), surfactant (e.g., polysorbate 20 or 80), and optionally, a thermal stabilizer (e.g., sucrose,

mannitol, sorbitol, or trehalose) and/or a viscosity reducing agent (e.g., arginine hydrochloride). Ex. 1001, 2:34-3:39.

97. The formulations disclosed in the patent contain high-concentrations VEGF receptor fusion protein generally between 40 - 275 mg/mL depending on the specific protein and therapeutic target and the patent references concentrations of 100 mg/mL – 126 mg/mL in the claims. Ex. 1001, 3:28-39, 61:51-61, 64:29-34. The patent describes several protein concentrations from 4 mg – 20 mg of VEGF fusion protein and the claims specifically refer to an 8 mg dose. Ex. 1001, 18:29-41, 61:51-61, 64:3-9, 64:16-22. This high concentration leads to “fewer possible injections per administration cycle.” Ex. 1001, 2:10-14. The specification acknowledges that “monthly or bi-monthly intravitreal injections represent a significant treatment burden on patients” and teaches dosing intervals as frequent as every 2 weeks or as infrequent as every 24 weeks. Ex. 1001, 30:6-14, 51:22-25.

98. The patent describes that the high concentration formulations also “allow for reduced ocular administration volumes, a benefit for avoiding undesired effects on the limited volume of the eye.” Ex. 1001, 2:29-33. The patent cites injection volumes of 70 microliters and 100 microliters in the claims and teaches

injection volumes between about 40 microliters to 100 microliters. Ex. 1001, 30:39-50, 61:51-61, 64:29-34.

99. These formulations are designed to be injected into the eye of a patient by intravitreal injection. Ex. 1001, 29:12-19. The patent teaches that “since small needle bores are preferred for performing intravitreal injections (due to decreased patient discomfort and eye trauma), a relative low viscosity is desirable.” Ex. 1001, 13:33-36. Further, “a lower viscosity formulation requires less force to push the formulation through the needle, thus making injection of the formulation through the needle easier for the treating physician.” Ex. 1001, 13:36-39. The specification teaches that an aqueous formulation with a viscosity of 5-15 centipoise (cP) at 20 °C is typical and “can also have a pharmaceutically acceptable viscosity for ocular administration, for example, intravitreal injection.” Ex. 1001, 20:14-30. A viscosity range of 5-15 centipoise (cP) at 20 °C is also reflected in the claims. Ex. 1001, 61:51-61, 62:52-62.

100. The '036 patent describes the benefits of a higher concentration of the VEGF receptor fusion protein formulations which include “shorter injection times, smaller injection volumes, lower frequency of antibody administration, and more efficient manufacturing and storage utility.” Ex. 1001, 1:55-1:58. The patent

describes obstacles to developing this formulation such as “increased protein aggregation and viscosity, which results in lower overall antibody or protein potency, and lower manufacturing and poorer storage stability.” Ex. 1001, 1:61-65.

101. The patent purports to describe solutions to these obstacles. The inventors screened combinations of ingredients (e.g., buffers, sugars, surfactants, and viscosity-reducing agents) to identify formulations that maintain stability and acceptable viscosity. Ex. 1001, 1:42-2:40, 46:29-51:14. The patent describes that the histidine buffer was found to lower viscosity compared to phosphate buffer. Ex. 1001, 13:20-33. Further, the '036 patent describes that the inclusion of arginine hydrochloride in a histidine buffer improved stability at refrigerated temperatures, despite being destabilizing at higher (stress) temperatures. Ex. 1001, 13:2-33. The patent describes that arginine initially appeared to “decrease stability when under temperature stress” rather than increase stability. Ex. 1001, 13:20-24. Non-ionic surfactants (e.g., polysorbate 20) and sugars (e.g., sucrose) were included to further reduce aggregation and stabilize the protein. Ex. 1001, 19:12-29. Stability and viscosity were validated through empirical testing, including real-time and accelerated stability studies. Ex. 1001, 34:29-58:45.

VIII. THE '036 PROSECUTION HISTORY

102. The application that led to the '036 patent was filed on July 23, 2021, as U.S. Patent Application No. 17/384,070 (“the '070 application”). I understand from Alvotech’s counsel that the '070 application claimed priority to provisional application No. 62/669,506 (“the '506 provisional”), filed on May 10, 2018.

103. During prosecution of the '036 patent, the examiner issued a non-final rejection on March 22, 2023 raising several objections and rejections. EX1002 (March 22, 2023, Non-Final Rejection) at 2140-2148.

104. The examiner rejected all claims under 35 U.S.C. § 112(b) for indefiniteness citing to the phrase “at least about” which was present in the sole independent claim at the time. EX1002 (March 22, 2023 Non-Final Rejection) at 2143. The examiner argued that the specification does not provide any “indication as to what range is covered by the term.” EX1002 (March 22, 2023 Non-Final Rejection) at 2143.

105. The examiner also rejected the claims under 35 U.S.C. § 112(a) for lack of written description stating “the claim recites a high concentration of a VEGF receptor fusion protein without any recitation of the elements of the composition that permit such a high concentration of the protein.” EX1002 (March

22, 2023 Non-Final Rejection) at 2145. The examiner explained the specification of the '036 patent “does not provide adequate written description for the breadth of the formulation encompassed by the claims.” EX1002 (March 22, 2023 Non-Final Rejection) at 2145.

106. Finally, the examiner rejected the pending claims based on nonstatutory double patenting asserting that they are unpatentable over the claims of U.S. Pat. No. 11,103,552 (“the '552 patent”) because the claims overlap in scope. EX1002 (March 22, 2023 Non-Final Rejection) at 2146.

107. The PO filed a response on August 1, 2023. EX1002 (Aug. 1, 2023 PO Response) at 756-766. In response to the examiner’s 35 U.S.C. § 112(b) indefiniteness rejection, PO argued there is support in the specification for “at least about” where it states “about” means “the value may vary from the recited value by no more than 1 %.” EX1002 (Aug. 1, 2023 PO Response) at 764; Ex. 1001, 13:52-55. PO further argued “the meaning of term would be clear to a practitioner of ordinary skill in the art.” EX1002 (Aug. 1, 2023 PO Response) at 764. In response to the examiner’s 35 U.S.C. § 112(a) rejection for lack of written description, the PO amended the claims to include protein concentration ($\geq$ 100mg/ml), injection volume ($\leq$ 100 microliters) and viscosity (about 5-15 cP at

20°C) asserting that the formulation specified in the amended claim is “optimal for delivery of at least 8 mg of VEGF receptor fusion protein.” EX1002 (Aug. 1, 2023 PO Response) at 764. In response to the examiner’s double patenting rejection, the PO filed a terminal disclaimer limiting the term of the ’036 patent to the expiration date of the ’552 patent. EX1002 (Terminal Disclaimer) at 749-753.

108. The PO also added new claims and cited to corresponding support in the specification. EX1002 (Amendment to Claims) at 758-762. This included a new independent claim which specifies 103 mg/mL – 126 mg/mL of aflibercept with viscosity of 5 cP – 15 cP at 20°C. EX1002 (Amendment to Claims) at 761-762.

109. The examiner filed a notice of allowance on September 1, 2023 in which the examiner withdrew all pending objections and rejections and allowed the claims. EX1002 (Sept. 1, 2023 Notice of Allowance Cont. Sheet,) at 694-695. The examiner withdrew the 112(b) rejection because of PO’s amendment, cancellation of certain claims, and argument there was a limiting definition for “at least about” in the specification. EX1002 (Sept. 1, 2023 Notice of Allowance) at 694-695. The examiner withdrew the 112(a) rejection because of the amendment, cancellation of certain claims, and argument that the amended claim specifies the

necessary components to support use of a high concentration of VEGF receptor fusion protein. EX1002 (Sept. 1, 2023 Notice of Allowance) at 695. Further, the examiner withdrew the double patenting rejection in light of the PO's terminal disclaimer. EX1002 (Sept. 1, 2023 Notice of Allowance, Sep 2023) at 694-695. The examiner allowed the claims and the '036 patent issued on December 17, 2024. EX1002 (Notice of Allowance, Sep 2023) at 694-695.

IX. LEGAL STANDARDS

110. I am not an attorney, and I will offer no opinion on the law. I am, however, informed by Counsel and understand several principles concerning patentability that I have used in arriving at my opinions.

111. I understand from Counsel that the earliest effective filing date of the '036 patent is May 10, 2018, the date the first provisional patent application in this patent family was filed.

A. Interpretation of the Claims

112. I have been informed by counsel for Alvotech that for purposes of my analysis, the terms appearing in the '036 patent claims should be interpreted according their ordinary and customary meaning as understood by a POSA in view of the patent's disclosure and prosecution history. In that regard, I understand that

the best indicator of claim meaning is its usage in the context of the patent specification as understood by a POSA.

113. I further understand that the words of the claims should be given their plain meaning unless that meaning is inconsistent with the patent specification or the patent's history of examination before the Patent Office. I also understand that the words of the claims should be interpreted as they would have been interpreted by a POSA as of the effective filing date of the claimed invention.

114. In my opinion, the terms of the '036 patent do not need further construction and should be viewed in accordance with their plain and ordinary meaning.

B. Prior Art

115. I have been informed by counsel for Alvotech that that prior art is the body of knowledge publicly available to a person skilled in the field of the invention, including what would be obvious from it, at the time the invention was made.

116. I understand that documents and materials that qualify as prior art can be used to invalidate a patent claim as anticipated or as obvious.

C. Obviousness

117. I have been informed by Counsel and understand that documents and materials that qualify as prior art can render a patent claim unpatentable as obvious under 35 U.S.C. § 103. Further, I understand that a claim is unpatentable for obviousness “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.”

118. Counsel for Alvotech has informed me that when assessing whether a claim is obvious, I should consider: (i) the scope and content of the prior art; (ii) the level of ordinary skill in the art; (iii) the differences between the prior art and what is claimed; and (iv) any “secondary” evidence that may indicate that the claims are not obvious.

119. I understand all prior art references are to be looked at from the viewpoint of a POSA at the time of the invention, and that this viewpoint prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

120. I understand that a claimed invention may be obvious when there is some reason, suggestion, or motivation that would have led a POSA to modify a prior-art reference or to combine prior-art teachings to arrive at the claimed invention.

121. I understand that when a patented invention is a combination of known elements, a court must determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue by considering the teachings of prior art references, the effects of demands known to people working in the field or present in the marketplace, and the background knowledge possessed by a person having ordinary skill in the art.

122. I understand that disclosure of a range full within a broader claimed range renders the claimed range obvious.

123. My understanding is that prior art teachings are properly combined where a POSA having the understanding and knowledge reflected in the prior art and motivated by the general problem facing the inventor, would have been led to make the combination of elements recited in the claims. Under this analysis, the prior art references themselves, or any need or problem known in the field of

endeavor at the time of the invention, can provide a reason for combining the elements of multiple prior art references in the claimed manner.

124. I further understand that in combining or modifying prior-art references to arrive at the claimed invention, a POSA must also have a reasonable expectation of success, given their general knowledge and what has been disclosed in the prior art. It's my understanding that this success need only be reasonably expected and does not need to be guaranteed or proven.

X. PRIOR ART TO THE '036 PATENT

125. I understand that each of the references discussed below are prior art to the '036 patent because they were published more than one year prior to the May 10, 2018 priority date.

A. Vitti: U.S. Patent Publication No. 2016/0144025

126. Vitti (US 2016/0144025) is the publication of U.S. patent application no. 14/943,490 that was filed by Regeneron on November 17, 2015. EX1007 at 1. Vitti is titled "Methods and Formulations for Treating Eye Diseases" and published on May 26, 2016. EX1007 at 1.

127. Vitti is generally directed to methods for treating, preventing or reducing the severity of an eye disease. EX1007 at Abstract, [0002], [0008]. Vitti

discloses using the invention to treat several different eye diseases or disorders, including diabetic retinopathy, diabetic macular edema, age-related macular degeneration, retinal neovascularization, central retinal vein occlusion, branched retinal vein occlusion, polypoidal choroidal vasculopathy, and choroidal neovascularization. EX1007 at [0017].

128. Vitti discusses aflibercept as the “standard of care treatment” for neovascular AMD and DME, and that DME “is a manifestation of DR.” EX1007 at [0004], [0006]. Aflibercept is one of the two active ingredients in Vitti’s proposed treatment. EX1007 at [0127], [0135], [0139], [0141-0165] Instead of using the known-aflibercept for treating these diseases, Vitti explored a potential “synergistic activity to treat” eye disorders including diabetic retinopathy, DME, and AMD using VEGF antagonist (e.g., aflibercept) “in combination with” and another compound called angiopoietin-2 (Ang-2) inhibitor. EX1007 at [0002], [0022], [0088], [0090]. Vitti explains that “the phrase ‘in combination with’ means that the pharmaceutical composition comprising an Ang-2 inhibitor is administered to the subject at the same time as, just before, or just after administration of the VEGF antagonist.” EX1007 at [0061]. And only in some embodiments is the VEGF antagonist “administered as a co-formulation with the

Ang-2 inhibitor.” EX1007 at [0063]. Regarding administration, Vitti teaches that the formulation(s) are administered intravitreally. EX1007 at [0050]. In some embodiments “the Ang-2 inhibitor is administered [intravitreally] as a single combined dosage formulation with the VEGF antagonist.” EX1007 at [0050]. And in some embodiments the Ang-2 inhibitor is administered intravenously “and the VEGF antagonist is administered intravitreally.” EX1007 at [0050]. A person of skill in the art would therefore read Vitti and understand it is teaching aflibercept formulations (without the Ang-2 inhibitor) administered intravitreally as part of the combination treatment of the invention.

129. Vitti disclosed that a VEGF antagonist “comprise[s] two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also referred to as Flt1) and/or VEGFR2 (also referred to as Flk1 or KDR), and may also contain a multimerizing domain (e.g., an Fc domain which facilitates the multimerization [e.g., dimerization] of two or more chimeric polypeptides).” EX1007 at [0086]. A POSA would have understood that Vitti also exemplifies VEGFR1R2-Fc Δ C1(a) as a specific VEGF antagonist known as aflibercept and marketed as Eylea®. EX1007 at [0086].

130. Regarding the aflibercept portion of the treatment, Vitti describes in certain embodiments that the VEGF antagonist (aflibercept) is provided at a concentration of from 5 mg/mL±0.75 mg/mL to about 100 mg/mL±15 mg/mL. EX1007 at [0027], [0094], [0095]. Vitti goes on to disclose that formulation of the present invention may comprise “about 100 mg/mL of a VEGF antagonist such as aflibercept.” EX1007 at [0094],[0086] (describing aflibercept, marketed as EYLEA®, as an exemplary VEGF receptor-based chimeric molecule), [0089] (noting combination therapies as described may include a VEGF antagonist, for example, aflibercept, a VEGF-Trap). Vitti also points the reader to the Furfine (US Patent No. 7,608,261) for more discussion of exemplary formulations comprising a VEGF antagonist. EX1007 at [0107].

131. Among other disclosures, Vitti teaches that the described compositions can be intravitreally injected by drawing up the injection from a vial or by using a pre-filled syringe. EX1007 at [0040]-[0041].

132. Vitti proceeds to describe liquid volumes for intravitreally administration. EX1007 at [0127]. Specifically, Vitti states “[i]n certain embodiments, the liquid formulation comprising of from 10 mg/mL to 120 mg/mL of anti-Ang-2 antibody and from 10 mg/mL to 100 mg/mL of aflibercept is

comprised in a prefilled syringe and is administered intravitreally in a volume of approximately up to 100 μ L.” EX1007 at [0127].

133. The discussions in Vitti regarding volume are applicable to whether the formulation is aflibercept alone or aflibercept and Ang-2. The volume of the injection impacts the concentration and also, practically, the resulting IOP in the eye. A person of skill in the art would recognize the teachings regarding volumes for injection intravitreally up to 100 uL to be applicable to both formulations (aflibercept-alone or aflibercept-Ang-2).

134. Vitti also describes contemplated doses for the Ang-2 inhibitor and VEGF antagonist. EX1007 at [0139]. With respect to the VEGF antagonist, Vitti expressly discloses the use of “0.05 mg to about 10 mg of a VEGF antagonist (e.g., aflibercept)” in certain embodiments. EX1007 at [0139].

B. AU Eylea® Label (EX1009)

135. The “AU Eylea® label” is a product information document for Eylea® as approved by Therapeutics Goods Administration (“TGA”)—which is the equivalent to FDA in Australia. I understand from counsel that the “AU Eylea® label” was publicly available on the website for Regeneron’s Ex-US commercialization partner for Eylea®, Bayer, as of at least March 8, 2017.

136. The AU Eylea® Label provides clinicians and patients product information for the TGA-approved 2 mg Eylea® (aflibercept). EX1009 at 1. The AU Eylea® Label describes aflibercept as “Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine-[human vascular endothelial growth factor receptor1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211’:214-214’)-bisdisulfide dimer.” EX1009 at 1.

137. The AU Eylea® Label describes several TGA-approved indications for Eylea®, including indications for the treatment of adults with “neovascular (wet) age-related macular degeneration (wet AMD),” “visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO),” and “diabetic macular oedema (DME).” EX1009 at 21. The AU Eylea® Label also provides clinical safety and efficacy data of Eylea® supporting its approval.

EX1009 at 8-23. Included in the clinical data reported in the AU Eylea® Label is safety and efficacy data from the VISTA and VIVID studies that POSA would understand as supportive of its ability to treat diabetic retinopathy. EX1009 at 21. Specifically, the label discloses that “[a]t week 52, 33.3% and 33.8% of 2Q4 patients, 27.7% and 29.1% of 2Q8 patients, and 7.5% and 14.3% of laser control patients in the VIVID^{DME} and VISTA^{DME} studies, respectively **experienced an improvement in the severity of diabetic retinopathy, as measured by a ≥ 2 step improvement in the diabetic retinopathy severity scale (DRSS).**” EX1009 at 21 (emphasis added). The AU Eylea® Label also discloses data from patients with “proliferative retinopathy.” EX1009 at 25. These diseases are treated by intravitreal injection using a 30-gauge needle. EX1009 at 31.

138. The AU Eylea® Label also discusses clinical trial dosing of aflibercept in doses greater than 2 mg in a section called “OVERDOSAGE.” The AU Eylea® Label describes that in clinical trials of Eylea®, “doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated.” EX1009 at 35. The AU Eylea® Label further states that “[o]verdosing was associated with increased injection volume and subsequently with increased intraocular pressure.” EX1009 at 35. It goes on to advise that “in case of

overdosage[,] intraocular pressure should be monitored” and further treating initiated, if necessary. EX1009 at 35.

C. Larson: U.S. Patent Pub. 2015/0071920

139. Larson et al is U.S. Patent Publication (2015/0071920) that published on March 12, 2015, titled “Liquid Protein Formulations Containing Water Soluble Organic Dyes.” EX1010 at 1.

140. Larson is generally directed to “[c]oncentrated, low-viscosity, low volume, liquid pharmaceutical formulations of proteins.” EX1010 at Abstract. Larson is more specifically directed to “low-viscosity liquid formulations of pharmaceutically important proteins, especially high-molecular-weight proteins, such as mAbs,” that can “improve injectability and/or patient compliance, convenience, and comfort.” EX1010 at [0016]-[0018]. Larson discloses that “[a]ny protein can be formulated,” by its teachings including a “high-molecular-weight proteins” defined as over 100 kDa. EX1010 at [0089], [0027], Abstract. “The protein can be...a fusion protein.” EX1010 at [0161]. Larson also identifies the fusion protein EYLEA® (aflibercept), “a recombinant fusion protein . . . formulated as an iso-osmotic solution for intravitreal administration” as a suitable protein for its disclosed formulations. EX1010 at [0161], [0167].

141. These high-concentration, low-viscosity liquid formulations have protein concentrations “between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL.” EX1010 at [0022].

142. Larson teaches that its formulations are administered “using an 18-32 gauge needle” and that “[p]referred needle gauges for the delivery of the low-viscosity formulations include 27, 29, and 31 gauge, optionally thin walled.” EX1010 at [0079]. Larson further contemplates administration via “subcutaneous, intramuscular, or other types of injection.” EX1010 at [0224], [0234].

143. Larson teaches a target viscosity for administering high-concentration proteins through “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.” EX1010 at [0075], [0077]. Larson teaches this viscosity target for a wide variety of proteins, including known anti-VEGF drugs, Eylea® and ranibizumab. EX1010 at [0089], [0158], [0161], [0167].

144. Larson goes on to disclose and claim one way of achieving these target viscosities for high concentration proteins used in injections, recognizing there were other existing ways of lowering viscosity for high concentration proteins described in the art. EX1010 at [0008]-[0013]. Larson’s solution is to use water soluble organic dyes to adjust the viscosity. EX1010 at [0021].

D. Furfine: US Patent No. 7,608,261 (EX1005)

145. Furfine (US Patent No. 7,608,261) is a patent issued from U.S. patent application no. 11/818,463 that was filed by Regeneron on June 14, 2007. EX1005 at 1. Furfine is titled “VEGF Antagonist Formulations Suitable for Intravitreal Administration” and issued on October 27, 2009. EX1005 at 1.

146. Furfine generally describes ophthalmic formulations, including liquid formulations, of a VEGF-specific fusion protein antagonist suitable for intravitreal administration to the eye. EX1005 at Abstract, 1:17-24. The VEGF antagonist described in Furfine—SEQ ID NO: 4—is aflibercept. EX1005 at 1:32-37, 1:58-2:3, 5:63-6:8. A POSA would understand the VEGF antagonist described in Furfine to be aflibercept given its description of the fusion protein as comprising “a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component (also termed a “VEGF trap”). EX1005 at 1:59-64.

147. Furfine discloses embodiments of “a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist” among other ingredients. EX1005 at 2:4-6, 2:49-51, at claim 1.

Furfine also describes embodiments of where “the VEGF antagonist (SEQ ID

NO:4) is present at a concentration of about 10 to about 80 mg/ml.” EX1005 at 2:55-57,3:24-26, 3:29-31, claim 4.

148. Furfine teaches that the described ophthalmic formulations are provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration. EX1005 at 4:65-67.

E. Dix: US Patent No. 8,921,316 (EX1006)

149. Dix (US Patent No. 8,921,316) is a patent issued from U.S. patent application no. 13/909,745 that was filed by Regeneron on June 4, 2013. EX1006 at 1. Dix is titled “Stable Liquid VEGF Antagonist Formulations” and issued on December 30, 2014. EX1006 at 1.

150. Dix generally describes, like Furfine, ophthalmic formulations, including stable liquid formulations, of a VEGF-specific fusion protein antagonist suitable for intravitreal administration to the eye. EX1006 at Abstract, 1:50-55. The VEGF antagonist described in Dix—SEQ ID NO: 4—is aflibercept. EX1006 at 1:56-66, 2:61-63, 5:15-26. A POSA would understand the VEGF antagonist described in Dix to be aflibercept given its description of the fusion protein as comprising “a receptor component consisting essentially of an immunoglobulin-

like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.” EX1006 at 1:57-61.

151. Dix teaches embodiments what it terms “a high concentration stable liquid formulation of a VEGF antagonist” which includes 50-100 mg/ml of the fusion protein. EX1006 at 2:12-21. These embodiments are also reflected in the language of claim 1 which recites in part “[a] stable liquid formulation of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist comprising 10-100 mg/ml of a fusion protein comprising amino acids 27-457 of SEQ ID NO: 4.” EX1006 at claim 1.

152. In Example 4 of Dix, the inventors investigated higher concentration liquid formulations of a VEGF trap for stability. EX1006 at 10:1-55. Dix describes “[i]n one embodiment of a liquid formulation, the formulation comprises 10 mM histidine, 50 mM NaCl, 5-20% sucrose, 50-100 mg/ml VEGF trap, and one of 0.1% polysorbate 20 or 3% PEG 3350. EX1006 at 10:9-12. Dix details a benefit of the tested formulation in that “it provides a higher concentration of VEGF trap without requiring the manufacture of a lyophilized product.” EX1006 at 10:12-14.

153. Claim 1 of Dix claims “A stable liquid formulation” of 100 mg/mL of a VEGF antagonist. EX1006 at 19:38-42.

F. Fiedler U.S. Patent Pub. US 2017/0232199

154. Fiedler (US 2017/0232199) is the patent publication of PCT/EP2015/060514 published on August 17, 2017. EX1011 at 1. Fiedler is titled “Pre-Filled Plastic Syringe Containing a VEGF Antagonist.” EX1011 at 1. Fiedler generally describes a prefilled syringe containing a VEGF antagonist used for the treatment of ocular disease. *See* EX1011 at Abstract.

155. One of the VEGF Antagonists described in Fiedler is aflibercept. EX1011 at [0003]. Fiedler states that “[a]flibercept, marketed under the name Eylea®, is a recombinant fusion protein consistent of the VEGF binding portion from the extracellular domains of human VEGF receptors 1 and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin.” EX1011 at [0003]. Fiedler goes on to teach aflibercept as a more preferred anti-VEGF antagonist for use in the invention and that preferably its “concentration is 1 to 100 mg/ml.” EX1011 at [0018], [0019].

156. Fiedler contemplates administering the described aflibercept in a formulation to patients. EX1011 at [0029]. Fiedler teaches that “[p]referably, a

volume of 30 to 100 ul of the liquid formulation is administered to the patient.”

EX1011 at [0029]. Fiedler further disclosed that a most preferable injection volume “administered to the patient is 0.05 ml” which equates to 50 ul. EX1011 at [0067].

157. Fiedler further teaches administration of these aflibercept formulations to a patient “preferably having an ocular disease selected from the group consisting of age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RO), diabetic retinopathy in patients with diabetic macular edema or visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia.” EX1011 at [0028],[0082]. Fiedler further teaches that “[f]or intravitreal administration the needle size is typically 30 gauge, although 31-, 32, 33-, and 34-gauge needles may also be used.” EX1011 at [0052].

G. 2011 Eylea® Clinical Review

158. The 2011 Eylea® Clinical Review (also referred to as “Eylea® Clinical Review” or “Clinical Review”) summarizes FDA’s review of clinical

information supporting the United States approval of 2 mg Eylea® (aflibercept). EX1008.

159. The Eylea® Clinical Review summarizes the pharmacological and biopharmaceutical findings from several Eylea® clinical trials. EX1008 at 2-3. The Clinical Review disclosed “aflibercept was not observed to cause increases in DBP [diastolic blood pressure] or SBP [systolic blood pressure]” following intravitreal administration. EX1008 at 10-11 (Fig.2.2.4.2-1).

XI. GROUND 1: Claims 1 and 4-38 are obvious over the Combination of Vitti, AU Eylea® Label, and Larson

160. In my opinion, a POSA would have found methods for treating an angiogenic eye disorder using a high concentration and a high dose of a VEGF receptor fusion protein as recited in claims 1 and 4-38 of the '036 patent obvious before May 2018. Specifically, a POSA would have been motivated to combine Vitti, the AU Eylea® label, and Larson to alleviate the treatment burden associated with repeat intravitreal injections by developing methods of treating angiogenic eye disorders with high concentrations (at least 100 mg/ml) of a VEGF antagonist (including aflibercept) that would allow for administration of a high dose (at least about 8 mg). And a POSA would have had a reasonable expectation of success in doing so in light of the combined teachings of Vitti, the AU Eylea® label, and

Larson, which together teach and/or make obvious each and every limitation of claims 1 and 4-38.

A. A POSA Would Have Been Motivated to Combine Vitti, the AU Eylea® label, and Larson with a Reasonable Expectation of Success

161. Protein-based pharmaceutical drugs have evolved over the past two decades. A desire to decrease patient burden including by administering higher doses of protein-based pharmaceutical drugs to patients has guided this evolution. A challenge to the development of higher doses of protein-based pharmaceutical drugs that require intravitreal administration included limits on intravitreal injection volume, which requires an increase in protein concentration as compared to lower doses. The increase in protein concentration results in an increase in viscosity, and there are limits to the viscosity of high concentration protein-based pharmaceutical drugs based on the physical constraints of pushing the formulation through a small-bore needle for patient administration. A POSA would have recognized that the solution for this problem was already set forth in the prior art, as disclosed in Vitti and the AU Eylea® Label, which were informed by the target viscosity disclosures for high concentration proteins in Larson.

162. By way of background, a POSA would have understood that patients receiving long-term, frequent intravitreal injections face considerable logistical, emotional, and financial burdens. EX1047 at S3. Indeed, a POSA would have been aware that many patients express fears of having injections in the eye, anticipating pain or discomfort. EX1047 at S8. Further, due to age-related challenges, many patients also have difficulty arranging and travelling to appointments for treatment and monitoring. EX1047 at S8. This is unsurprising given that “[i]n a survey of 75 patients with nAMD (mean age=79 years), the reported mean time per visit was 11.7 hours, accounting for appointment preparation, travel, waiting time, treatment time, and post-appointment recovery.” EX1047 at S8. In that same study, “[m]ost patients (72%) reported that they were driven to their appointments by a caregiver, requiring a significant amount of caregiver time away from work or personal activities.” EX1047 at S8.

163. A POSA would further understand that the treatment burden of long-term, frequent intravitreal injections extends to care providers in addition to patients. Specifically, treatment and follow-up monitoring of patients receiving long-term, frequent intravitreal injections can pose considerable burden on physicians and their clinical staff. EX1047 at S8. In one survey, “67% of the

physicians indicated that it would be very desirable to reduce the number of office visits for the treatment and monitoring of patients with nAMD.” EX1047 at S8. These burdens for patients and caregivers led to patients skipping intravitreal injections and/or quitting treatment over time, causing their angiogenic eye disorders to worsen.

164. To address these widely understood treatment burden issues, a POSA would be aware that clinicians had explored various strategies to reduce the number of patient visits and injections including alternative dosing strategies including extended dose intervals, treat-and-extend, pro re nata (PRN) dosing, and interleaving a second anti-VEGF agent at shorter intervals than suggested for a single agent. EX1047 at S8 (discussing quarterly fixed-interval dosing protocol); EX1039 at 1183 (discussing treat-and-observe (PRN) and treat-and-extend protocols); EX1023 at 1; EX1026 at 1. These efforts are described in more detail in Section V.F above.

165. One reason why a POSA would be interested in higher concentrations, is that higher concentrations could allow for higher dose administered. For these types of proteins, a POSA would recognize that higher dose has benefits and limited, if any, safety concerns. Vitti also teaches a POSA high doses of

aflibercept. Specifically, Vitti aflibercept teaches doses of “0.05 mg to about 10 mg of a VEGF antagonist (e.g., aflibercept).” EX1007 at [0139].

166. High doses of aflibercept and other similar proteins was something a POSA would be interested in. The field was investigating ways to reduce the frequency of administration by increasing the dosage. EX1039 at 1183 (studies showed that decreases the number of intravitreal injections decreases the cumulative incidence of ocular complications for a patient); EX1026 at 1 (HARBOR study comparing 0.5 mg to 2.0 mg of ranibizumab with results showing increased dosage of anti-VEGF drug has a greater effect on durability than efficacy and showing no new safety events with four-fold increase in dosage). These efforts are described in more detail in Section V.F above.

167. A POSA would further understand that researchers in the field were specifically looking to address the unmet need of optimizing aflibercept delivery by using higher dosage. EX1035 at 586-587 (evaluating the safety, tolerability, and bioactivity of 0.15 mg and 4 mg doses of aflibercept). Nguyen showed in the Phase I CLEAR-IT 1 trial that the safety and tolerability of 0.15 mg and 4 mg doses of aflibercept were identical. EX1035 at 586. Nguyen 2012 specifically suggested that “[a]n improvement to the current therapeutic options would be to

increase the duration of drug activity, so that intravitreal injections can be administered less frequently” and stated that the study results “help to provide uncontroversial support for a dose-response effect of intravitreal aflibercept in neovascular AMD” noting equal importance in the “lack of any increase in AEs associated with the higher dose, suggesting that the higher dose of intravitreal aflibercept may have increased bioactivity, but did not carry additional risks of deleterious effects during the 8-week study.” EX1035 at 587. This is consistent with Regeneron’s prior disclosures in a March 8, 2006 presentation at the Lehman Brothers 9th Annual Global Healthcare Conference where Regeneron reported on a Phase I trial evaluating 0.05, 0.15, 0.5, 1.0, 2.0, and 4.0 mg doses of intravitreal aflibercept. EX1030 at 18. Regeneron reported as a result of this study that “maximum tolerated dose [for aflibercept was] not reached.” EX1030 at 18.

168. A POSA would also have seen Regeneron report on clinical trials where doses greater than 4 mg—8 mg doses—were administered to a handful of patients. The AU Eylea® Label describes in the “OVERDOSAGE” section that in clinical trials of Eylea®, “doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated.” EX1009 at 35. This is consistent with toxicology data generated by Regeneron which found that drug-

toxicity-related adverse events were only observed at exceedingly high doses when tested in monkeys, which I discuss further below. The Label further states that “[o]verdosing was associated with increased injection volume and subsequently with increased intraocular pressure.” EX1009 at 35. It goes on to advise that “in case of overdose[,], intraocular pressure should be monitored” and further treating initiated, if necessary. EX1009 at 35. A POSA would have understood that the increased intraocular pressure was associated with the increased injection volume not the 8 mg dose of aflibercept.

169. A POSA would thus have been motivated to develop high doses of aflibercept (in other words at the high end of Vitti’s disclosed acceptable range) given the desire to reduce frequent, burdensome intravitreal injections for various angiogenic eye disorders, including AMD, DME, and DR. In particular, a POSA would have been motivated to target an 8 mg dose in view of the AU Eylea® Label. A POSA would have had a reasonable expectation of success in targeting an 8 mg dose given Regeneron’s disclosures that the maximum tolerated dose had not yet been achieved after dosing patients with 4 mg, which was safe, effective, and well tolerated per Nguyen 2012, and that 8 mg (doubling the 4 mg dose in Nguyen) was generally well tolerated per the AU Eylea® Label. EX1035;

EX1030 at 18. A POSA would have also had reasonable expectation of success in increasing the dose of low dose Eylea® (2 mg) four-fold from the HARBOR study, which demonstrated a 4x dose of ranibizumab was tolerated, efficacious, and had increase durability. EX1026; EX1039.

170. A POSA would have further believed an 8 mg dose of aflibercept would be capable of treating patients with AMD, DME, and DR given the clinical trial discloses in the AU Eylea® Label. For example, the AU Eylea® Label describes several TGA-approved indications for low dose (2 mg) Eylea®, including indications for the treatment of adults with “neovascular (wet) age-related macular degeneration (wet AMD),” “visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO),” and “diabetic macular oedema (DME).” EX1009 at 21. The AU Eylea® Label also provides clinical safety and efficacy data of Eylea® that POSA would understand as supportive of its ability to treat diabetic retinopathy. EX1009 at 21. Specifically, the label discloses that “[a]t week 52, 33.3% and 33.8% of 2Q4 patients, 27.7% and 29.1% of 2Q8 patients, and 7.5% and 14.3% of laser control patients in the VIVID^{DME} and VISTA^{DME} studies, respectively **experienced an improvement in the severity of diabetic retinopathy, as measured by a ≥ 2 step improvement in**

the diabetic retinopathy severity scale (DRSS)." EX1009 at 21 (emphasis added).

171. A POSA would have expected that a high-concentration aflibercept formulation allowing for a high dose would safely and effectively treat angiogenic eye disorders at least as well as low concentration, low dose aflibercept. A POSA would have known this is due in part to how aflibercept works. Aflibercept acts as a decoy receptor of "VEGF-trap." EX1009 at 1-3. This allows aflibercept to bind excess VEGF produced by the eye with a greater affinity than the eye's natural receptors. EX1009 at 3. With increasing doses of aflibercept, a POSA would have expected extended duration of action for aflibercept in the eye.

172. It was known in the art, as discussed by Stewart et al. 2012, that clinical data—including for aflibercept and ranibizumab (i.e. HARBOR study I discuss above)—suggested that "increasing the dose of a drug prolongs its duration of action (durability). EX1039 at 1182. This data was "consistent with previously published models which predict[ed] that increasing the dose of an effective anti-VEGF drug has a greater effect on its durability than its efficacy." EX1039 at 1182. In simpler terms, one can think of high doses of aflibercept as providing more aflibercept that sits in the eye longer than a lower dose and continues to bind

excess amounts of VEGF produced by the eye without negatively impact. A POSA would thus have expected a high dose of a high concentration aflibercept formulation to be at least as efficacious for treating angiogenic eye disorders, including AMD, DME, and DR, as low dose Eylea®.

173. As for safety, in addition to Regeneron's finding that 8 mg aflibercept was tolerable when clinically administered to patients with angiogenic eye disorders, a POSA would have further expected that an 8 mg dose of aflibercept was safe for treating these patients from Regeneron's disclosures of toxicity data for aflibercept.

174. Unlike intravenous injection of aflibercept, aflibercept administered by intravitreal administration is "slowly absorbed from the eye into the systemic circulation" and is "predominately observed in the system circulation as an active, stable complex with VEGF." EX1009 at 7. Studies disclosed in the AU Eylea® Label teach a POSA that low dose aflibercept was "undetectable two weeks following dosage in almost all patients" and "does not accumulate in the plasma." EX1009 at 7. The label further teaches that "systemic pharmacodynamic effects are unlikely." EX1009 at 8. As for toxicity, a POSA would not have been concerned with administering an 8 mg dose of aflibercept to treat AMD, DME, or

DR in view of Regeneron's toxicity data from study in monkeys. For example, Regeneron reported in a 2012 Assessment Report provided to the European Medicines Agency in support of Eylea®, that single-dose toxicity was evaluated in Cynomolgus monkeys following intravitreal administration of VEGF Trap (i.e., aflibercept). EX1058 at 19.

175. To develop a high concentration, 8 mg dose of aflibercept for intravitreal injection, a POSA working with a formulator would have recognized the need to increase concentration while balancing the well-known limitations of the amount of liquid a clinician could administered into a patient's eye.

176. A POSA would have been aware that Vitti is a Regeneron patent publication that teaches high concentration formulations of aflibercept for treating angiogenic eye disorders, including wet-age macular degeneration, diabetic macular edema, and diabetic retinopathy with high doses. EX1007 at [0135], [0004]-[0007], [0053]-[0056].

177. While Vitti explored the synergistic effect of combined therapy of an angiopoietin-2 (Ang-2) inhibitor with a VEGF antagonist (expressly including aflibercept—the “standard of care treatment for neovascular AMD and DME”) to treat angiogenic eye disorders, a POSA would have recognized that Vitti teaches

embodiments where a high concentration VEGF antagonist (e.g., aflibercept) is separately formulated and administered intravitreally whereas the Ang-2 inhibitor is administered intravenously or subcutaneously. EX1007 at [0006], [0018], [0022], [0050], [0088]. Thus, a POSA would have understood the disclosures in Vitti regarding a high dose, high concentration formulation of aflibercept for intravitreal administration to be particularly relevant.

178. Given the disclosures in Vitti about high concentrations and high doses of aflibercept, a POSA would have looked for other teachings about what high doses of aflibercept for administration to patients and well tolerated.

179. The POSA would have been motivated to search for other Regeneron high dose aflibercept disclosures in the art and turned to the AU Eylea® Label. The label taught that an 8 mg dose of aflibercept was “generally well tolerated” when administered to a limited number of patients. EX1009 at 35. While the disclosure of the administration of 8 mg doses of aflibercept in clinical trials evaluating angiogenic eye disorders is found in the “OVERDOSAGE” section of the label, a POSA would have immediately recognized any warnings in this section are not related to the dose. Rather, a POSA would have understood the concern with overdoses to be related to the increase in ocular pressure due to additional

volume of aflibercept injected. This is consistent with toxicology data generated by Regeneron which found that drug-toxicity related adverse events were only observed at exceedingly high doses when tested in monkeys. EX1058 at 20-21. It is also consistent with other Regeneron disclosures reporting that the maximum tolerated dose for intravitreal aflibercept had not yet been identified after testing dosages up to 4 mg. EX1030 at 14, 18. A POSA thus would have been motivated to combine the teachings of Vitti and the AU Eylea® Label to target an 8 mg dose of aflibercept.

180. A POSA would understand that a higher concentration formulation of aflibercept would be necessary to achieve a higher dose. Vitti teaches embodiments of highly concentrated liquid formulations of VEGF antagonists, including 10 ± 1.5 mg/mL to 100 ± 15.0 mg/mL. EX1007 at [0087], [0094],[0127]. Vitti also provides the POSA guidance on how to formulate high concentrations of aflibercept by suggesting the POSA follow other Regeneron prior art, including the teachings of Furfine. EX1007 at [0107] (“Exemplary formulations comprising a VEGF antagonist that can be used in the context of the present invention are disclosed, e.g., in U.S. Pat. Nos. 7,531,173 and 7,608,261.”) Thus, a POSA would

understand Vitti to teach high concentration liquid formulations of aflibercept (including up to 115 mg/mL) as a separate intravitreal dosage form.

181. It was well known in the art that intravitreally administering anti-VEGF drugs, including aflibercept, requires a small, gauged needle so as not injure or irritate the eye. This teaching is present in both Vitti and the AU Eylea® Label, further supporting the POSA's motivation to combine these references. For example, Vitti teaches that the liquid pharmaceutical formulations disclosed in are provided in a container, and identifies various embodiments of such containers. EX1007 at [0040], [0127]. A POSA would understand Vitti discloses the use of a 30-gauge thin wall needle for both glass vials and prefilled syringes. EX1007 at [0040], [0127]. Similarly, the AU Eylea® Label discloses that a "30 G x ½ inch injection needle should be used" for intravitreal injection of 2 mg aflibercept. EX1009 at 31, 34.

182. A POSA with the desire to target an 8 mg dose of aflibercept would have worked with a formulator to prepare a high concentration formulation capable of being administered through a 30G needle. A POSA would recognize that viscosity contributes to the overall consistency of a liquid formulation, and that a liquid with higher viscosity generally has a thicker consistency. From the

clinician's perspective, an aflibercept formulation that was too thick (i.e., viscous) necessitating additional force on the plunger to administer into the eye would raise the risk of physical trauma to the eye.

183. Larson's teachings are consistent with the clinician's perspective and teaches these very issues. A POSA would have understood from Larson that VEGF antagonist formulations are administered with small needle gauges making them appropriate for intravitreal use. EX1010 at [0224], [0234]. Specifically, Larson taught that "[p]referred needle gauges for the delivery of the low-viscosity formulations include 27, 29, and 31 gauge, optionally thin walled." EX1010 at [0079]. These needle sizes are consistent with those disclosed in Vitti and the AU Eylea® Label— as well as those used for commercially available intravitreally administered anti-VEGF products (i.e., ranibizumab (Lucentis®))—thus motivating a POSA to apply Larson's viscosity teachings. EX1007 at [0127]; EX1009 at 31, 34 ("For the intravitreal injection a 30 G x ½ inch injection needle should be used."); EX1055 at Section 2.6.

184. Larson taught preferred viscosities for administering high-concentration proteins, describing a most preferable viscosity of "even more preferably less than about 20 cP, or most preferably less than or about 10 cP, when

measured at 25° C.” EX1010 at [0075], [0077]. Larson teaches this preferred viscosity for a wide variety of proteins, including known anti-VEGF drugs, Eylea® and ranibizumab, further encouraging the POSA to view the preferred viscosities in Larson as applicable for intravitreal use (i.e., 30-gauge needles). EX1010 at [0089], [0158], [0161], [0167].

185. The POSA, relying on the formulator, would have sought out teachings in the art about administering high concentration proteins, like aflibercept, for use in needles suitable for intravitreal use. A POSA would have been informed by the broad teachings in Larson of a target viscosity for injecting high-concentration protein formulations through the small needles required for intravitreal administration. My understanding from Dr. Falconer is that formulators had several different ways to manage viscosity for intravitreal administration. EX1004, 52. Larson taught one way “to provide low-viscosity liquid formulations of pharmaceutically important proteins, especially high-molecular-weight proteins, such as mAbs,” that can “improve injectability and/or patient compliance, convenience, and comfort.” EX1010 at [0016]-[0018]. These high-concentration, low-viscosity liquid formulations have protein concentrations “between about 10

mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL.” EX1010 at [0022c].

186. Based on the above teachings in the art, in my opinion, a POSA would have had a motivation to combine Vitti and the AU Eylea® Label with the viscosity disclosures in Larson with a reasonable expectation of success of achieving method of treating angiogenic eye disorders utilizing high concentration formulations claimed in claims 1-38 of the '036 patent.

B. Independent Claim 1

187. Independent claim 1 recites the following:

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

EX1001 at claim 1.

188. In my opinion, a POSA would have had a reasonable expectation of success of developing a method of treating angiogenic eye disorders according to claim 1 in light of the disclosures of Vitti, the AU Eylea® Label, and Larson.

1. 1[A] A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject

189. In my opinion, both Vitti and the AU Eylea® Label taught “[a] method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject.”

190. A POSA would have understood that Vitti taught that “that “[a]nti-vascular endothelial growth factor (VEGF) therapy (e.g., aflibercept) is the standard of care treatment for neovascular” age-related macular degeneration (AMD) and diabetic macular edema (DME) both of which are angiogenic eye disorders. EX1007 at [0006], [0053]. A POSA would have further understood that Vitti shows that intravitreal administration of anti-VEGF therapies including aflibercept was well known in the field. EX1007 at [0007]. And Vitti expressly disclosed a method for treating an angiogenic eye disorder “compris[ing]

administering a single dose of a VEGF antagonist followed by one or more doses” of Ang-2 inhibitor. EX1007 at [0012].

191. The AU Eylea® label also taught treating humans with wet AMD, DME, and visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO), which are all angiogenic eye disorders, by administering aflibercept through intravitreal injection. EX1009 at 24, 29-30.

2. 1[B] in a volume of about 100 microliters or less

192. In my opinion, both Vitti and the AU Eylea® label taught “a volume of about 100 microliters or less.”

193. A POSA would have understood that Vitti disclosed liquid pharmaceutical formulations comprising aflibercept and an Ang-2 inhibitor administered for the treatment of angiogenic eye diseases. EX1007 at [0002], [0012], [0018], [0016], [0022], [0026], [0050], [0091]. And a POSA would understand that Vitti taught a volume of up to 100 µL for liquid formulations comprising from 10 mg/mL to 100 mg/mL of aflibercept in a prefilled syringe for intravitreal injection. EX1007 at [0127]. This is consistent with what a POSA would have understood as the acceptable range of intravitreal injection volumes:

20 uL to 100uL. EX1029 at 377. This is also consistent with the injection volumes for anti-VEGF products as shown above in Section V.E.1.

194. A POSA would have further understood that 0.1 ml (or 100 μ L) was considered the upper safe volume limit for a liquid formulation for intravitreal injection to the eye given the risks of increased intraocular pressure with intravitreal injections. EX1014 at S11. Indeed, I reported as part of an expert panel that “injection volumes in excess of 0.1 mL can produce dramatic increases in IOP.” EX1014 at S11. Thus, a POSA would limit the injection volume to no more than 0.1 mL.

3. 1[C] at least about 8 mg

195. In my opinion, both Vitti and the AU Eylea® label taught, or at least, rendered this limitation obvious.

196. Specifically, a POSA would have understood that Vitti disclosed “at least about 8 mg” through its teaching of certain embodiments in which the pharmaceutical formulations contain “ 5 ± 0.75 mg/mL to 100 ± 15 mg/mL of a VEGF antagonist.” EX1007 at [0094]. A POSA would have further understood that Vitti disclosed specific embodiments of “about 80 mg/ml,” “about 90 mg/ml,”

and “about 100 mg/mL” of a “VEGF antagonist such as aflibercept.” EX1007 at [0094].

197. A POSA would have taken Vitti’s disclosures and employed basic and routine mathematics to calculate the dosage (in mg) of aflibercept in each embodiment based on the POSA’s understanding, described above, that the injection volume should be limited to 100 microliters. For example, Vitti’s disclosure of a formulation with a VEGF antagonist concentration of 80 mg/mL contains “about 8 mg” aflibercept in a volume of 100 microliters ($80 \text{ mg/ml} \times 0.1 \text{ ml} = 8 \text{ mg}$). EX1007 at [0094]. Similarly, Vitti’s disclosure of a formulation with a VEGF antagonist concentration of 90 mg/mL contains “about 9 mg” aflibercept in a volume of 100 microliters ($90 \text{ mg/ml} \times 0.1 \text{ ml} = 9 \text{ mg}$). EX1007 at [0094]. Likewise, Vitti’s disclosure of a formulation with a VEGF antagonist concentration of 100 mg/mL contains “about 10 mg” aflibercept in a volume of 100 microliters ($100 \text{ mg/ml} \times 0.1 \text{ ml} = 10 \text{ mg}$). EX1007 at [0094]. A POSA would have understood that each of these disclosures in Vitti fall within the scope of “at least about 8 mg.” EX1007 at [0094].

198. In addition, the AU Eylea® Label teaches a POSA “at least 8 mg.” A POSA would understand that the AU Eylea® label disclosed that patients received

overdoses of 8 mg of aflibercept during clinical trials and that these overdoses were “generally well tolerated.” EX1009 at 35. While the AU Eylea® Label called these 8 mg doses “overdoses” (as the indicated treatment was 2 mg), the label does not suggest the 8 mg dose itself caused any concerns with efficacy or safety. A POSA would understand the only concern it identifies is increased interocular pressure from the “increased injection volume” associated with quadrupling the 2 mg dose (at 50 microliters) to 8 mg (which would be a volume of 200 microliters).

4. 1[D] of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component

199. In my opinion, Vitti, the AU Eylea® Label, and Larson taught this limitation at least because each discloses pharmaceutical formulations comprising a VEGF antagonist as recited in claim 1[D].

200. A POSA would have understood that Vitti disclosed that a VEGF antagonist “comprise[s] two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also referred to as Flt1) and/or VEGFR2 (also referred to as Flk1 or KDR), and may also contain a multimerizing domain (e.g., an Fc domain which facilitates the multimerization [e.g., dimerization] of two or

more chimeric polypeptides).” EX1007 at [0086]. A POSA would have understood that Vitti also exemplifies VEGFR1R2-FcΔC1(a) as a specific VEGF antagonist known as aflibercept and marketed as Eylea®. EX1007 at [0086].

201. A POSA would have further understood that the AU Eylea® label disclosed the structure of aflibercept, identifying it as “Vascular endothelial growth factor receptor type VEGFR-1 (synthetic human immunoglobulin domain 2 fragment) fusion protein with vascular endothelial growth factor receptor type VEGFR-2 (synthetic human immunoglobulin domain 3 fragment) fusion protein with immunoglobulin G1 (synthetic Fc fragment), dimer des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 C-terminal residues)-peptide (Fc fragment)], (211-211’:214-214’)-bisdisulfide dimer.” EX1009 at 1. The disclosures in the AU Eylea® Label and Larson are all consistent with how Regeneron characterized aflibercept to the Patent Office. Specifically, Regeneron stated “[t]he name of the approved product is EYLEA™. The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap,

VEGF Trap-Eye and VEGF-TRAPR1R2. Aflibercept is a fusion protein consisting of (a) a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Flk1; and (b) an Ig domain 3 of a second.” EX1013 at 2.

202. A POSA would have further understood that Larson described a number of fusion proteins and disclosed that “EYLEA (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fe portion of human IgG1.” EX1010 at [0164], [0167].

203. A POSA would have understood that the above disclosures of Vitti, the AU Eylea® Label, and Larson each taught the same VEGF antagonist fusion protein meeting this limitation.

5. 1[E] wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/mL of the VEGF receptor fusion protein

204. In my opinion, Vitti taught this limitation.

205. Specifically, a POSA would have understood that Vitti taught a “stable liquid pharmaceutical formulation” comprising VEGF antagonist, which may be “an aqueous solution . . . for IVT [intravitreal] administration.” EX1007 at

[0026], [0260]. A POSA would have further understood that Vitti taught that the “stable liquid pharmaceutical formulation” may comprise “ 10 ± 1.5 mg/mL to 100 ± 15.0 mg/mL” of VEGF antagonist and specifically discloses an embodiment comprising “about 100 mg/mL of a VEGF antagonist such as aflibercept.” EX1007 at [0087], [0094]. Vitti thus teaches formulations with “at least 100 mg/ml” VEGF antagonist, as claimed.

206. Further, as I discuss above in Section XI.A, a POSA would have sought to have a high concentration, on the upper end of what is disclosed in Vitti. I understand from counsel that because Vitti’s disclosure of 100 ± 15.0 mg/mL is itself a range (of 85 mg/ml to 115 mg/mL) and because that range overlaps with the claimed range, this limitation is presumptively obvious.

207. Similarly, I understand from counsel that this limitation is also presumptively obvious because Vitti’s “ 10 ± 1.5 mg/mL to 100 ± 15.0 mg/mL” disclosure overlaps with the claimed range of “at least 100 mg/ml.”

6. 1[F] and having a viscosity of about 5-15 centiPoise (cP) at 20°C

208. I understand from Dr. Falconer that a POSA would understand that Larson teaches “a viscosity of about 5-15 cP at 20°C.” EX1004, 123. For example, Larson disclosed that the liquid protein formulation resulting from its

platform would “most preferably” have a viscosity of “even more preferably less than about 20 cP, or most preferably less than or about 10 cP, when measured at 25°C” that could be administered using “a very small gauge needle, for example, between 27 and 31 gauge, typically 27, 29, or 31 gauge.” EX1010 at [0075], [0231]; EX1004, 123.

C. Dependent Claims 4-34

1. Claims 4-8

209. Each of claims 4-8 depend on claim 1 and recite various viscosities at 20° C for the formulations described in the method of claim 1. EX1001 at claims 4-8. Specifically, claim 4 recites “**about 10-13 cP,**” claim 5 recites “**about 11-12 cP,**” claim 6 recites “**about 12-15 cP,**” claim 7 recites “**about 5 cP,**” and claim 8 recites “**about 6 cP.**” EX1001 at claims 4-8.

210. I understand from Dr. Falconer that a POSA would know to apply the viscosity teachings of Larson to the 100 mg/mL aflibercept formulation taught in Vitti to achieve a viscosity of 5-15 cP at 20° C. EX1004, 125. I further understand from Dr. Falconer that a POSA would realize Vitti teaches the use of excipients to control the viscosity to create a stabilizing effect. EX1007 at [0096]; EX1004,

120. A POSA would look to Larson which teaches desired viscosities for high

concentration proteins, particularly “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.” EX1010 at [0075], [0077]; EX1004, 124.

211. I understand from Dr. Falconer that a POSA would know the viscosity of a liquid is a function of temperature where the viscosity of a solution decreases as temperature increases. EX1004, 124. Further, a POSA working with a formulator would be able to approximate the above noted preferred viscosities at 25°C to their values at 20°C using a mathematical equation (i.e., the Vogel-Fulcher-Tamman equation). EX1004, 124. According to Dr. Falconer, a POSA working with a formulator would be informed that the viscosity of a protein-containing solution at 25°C can be estimated to be approximately 1.126 times greater than the viscosity of the same solution at 20°C. EX1004, 124. Thus, a high concentration protein formulation, such as those described in Vitti and Larson, that had a viscosity of less than 20 cP at 25° C would have a viscosity of less than about 22.52 cP at 20° C. EX1004, 124. And such formulations with a viscosity of less than 10 cP at 25° C would have a viscosity of less than about 11.26 cP at 20° C. EX1004, 124.

212. Therefore, in my opinion, a POSA would understand with the aid of a formulator that Larson discloses viscosities at 20° C of “about 10-13 cP” recited by claim 4, “about 11-12 cP” recited by claim 5, “about 12-15 cP” recited by claim 6, “about 5 cP” recited by claim 7, and “about 6 cP” recited by claim 8. EX1001 at claims 4-8.

2. Claims 9, 10

213. Claims 9 and 10 depend on claim 1. EX1001 at claims 9, 10. Specifically, claim 9 requires the formulation described in the method of claim 1 **“comprises a sugar.”** EX1001 at claim 9. And claim 10 requires the formulation described in the method of claim 1 **“comprises sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol.”** EX1001 at claim 10.

214. A POSA working with a formulator would have understood that Vitti discloses adding a sugar (e.g., sucrose) to its pharmaceutical formulations, which I understand from Dr. Falconer. EX1004, 145; EX1007 at [33]. A POSA would further understand that Vitti directs a POSA to Furfine for “[e]xemplary formulations comprising a VEGF antagonist.” EX1007 at [107]; EX1004, 145.

215. A POSA working with a formulator would have further understood that Furfine discloses ophthalmic formulations optionally comprising a stabilizing

agent that may be sucrose. EX1005 at 2:15-16; EX1004, 145. I understand from counsel that because claim 10 recites specific sugars in the alternative, the disclosure of sucrose is sufficient to disclose a “formulation compris[ing] sucrose, trehalose, sorbitol, mannitol, propane, sulfonic acid or glycerol.” EX1001 at claim 10.

3. Claim 11

216. Claim 11 depends on claim 1. Claim 11 specifically requires that the formulation described in the method of claim 1 “**comprises an amino acid.**” EX1001 at claim 11.

217. A POSA would have understood that Vitti combined with Larson disclose an amino acid for use in a high concentration VEGF receptor fusion protein formulation as described in claim 11. I understand from Dr. Falconer, and as informed by my own review, Vitti discloses its pharmaceutical formulations may comprise “excipients” to “provide a desired consistency, viscosity or stabilizing effect.” EX1004, 149; EX1007 at [0096]. Vitti also discloses the use of a “buffer or buffer system,” which I understand from Dr. Falconer could be an excipient as Vitti describes in paragraph 96. EX1004, 149; EX1007 at [0106].

218. Larson discloses the use of “L-histidine buffer” in commercial therapeutic protein products. EX1010 at [0008]. L-histidine is an amino acid. I also note that in my review of Dix, it also discloses the use of histidine and glycine were in formulations comprising aflibercept, which Dr. Falconer confirms. EX1004, 149; EX1006 at Example 4-5, cl. 1.

4. Claim 12

219. Claim 12 depends on claim 1. Claim 12 requires that the VEGF receptor fusion protein described in the method of claim 1 is “**aflibercept.**” EX1001 at claim 12.

220. A POSA would have understood that both Vitti and the AU Eylea® label both disclose a VEGF receptor fusion protein that is aflibercept. For example, Vitti states “[a]n example of a VEGF antagonist that may be used in combination with the anti-Ang-2 antibodies in the method of treatment of the present invention is aflibercept, a VEGF-inhibiting fusion protein.” EX1007 at [0022],[0086], [0089]. Similarly, the AU Eylea® Label states that “Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.” EX1009 at 2. The disclosures in the AU Eylea® Label and Larson are consistent with how

Regeneron characterized aflibercept to the Patent Office. Specifically, Regeneron stated “[t]he name of the approved product is EYLEA™. The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAPR1R2. Aflibercept is a fusion protein consisting of (a) a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Flk1; and (b) an Ig domain 3 of a second.” EX1013 at 2.

5. Claim 13

221. Claim 13 depends on claim 1. Claim 13 requires that the angiogenic eye disorder described to be treated in the methods of claim 1 is one of the following disorders: **“age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DMA), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization,**

pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy, and/or proliferative diabetic retinopathy.”

EX1001 at claim 13.

222. A POSA would have understood the use of aflibercept for treating angiogenic eye disorders was well known as of May 2018. EX1009 at 24. For instance, a POSA would have understood that the AU Eylea® label discloses that aflibercept is indicated in adults for the treatment of wet AMD, CRVO, and DME, and also treats DR. EX1009 at 18-21, 24.

223. I understand from counsel that the use of the disjunctive “and/or” in claim 13 creates alternative subsets of claim coverage. Accordingly, I understand that the AU Eylea® Label’s disclosure of treating wet AMD with aflibercept satisfies the requirements of claim 13.

224. Further, a POSA would have considered it obvious and would have expected that high-dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including AMD and DME. Specifically, a POSA would have understood Vitti disclosed: a high-dose formulation of VEGF antagonist, including an embodiment of about 100 mg/ml VEGF antagonist. EX1007 at [0087], [0094]. A POSA would further have understood Vitti disclosed that the

“present invention” allows for the treatment of angiogenic eye disorders by administering a single dose of a VEGF antagonist followed by one or more doses of a pharmaceutical formulation comprising Ang-2 inhibitor. EX1007 at [0012]. A POSA would understand that Vitti contemplates the treatment of AMD and DME, the latter of which is a manifestation of diabetic retinopathy. EX1007 at [0066].

225. In addition, a POSA would have understood Vitti’s disclosure of the additional step of treating with Ang-2 following treatment with a VEGF antagonist does not mean that Vitti’s teachings do not apply including because (as I understand from counsel) claim 1 does not exclude steps not recited in the claims which is indicated by its use of the term “comprising.”

6. Claims 14, 15

226. Claim 14 depends on claim 13, which in turn depends on claim 1. Claim 14 requires that the angiogenic eye disorder treated using the methods of claims 1 and 13 is “wet age-related macular degeneration,” also known as wet AMD. EX1001 at claim 14. Claim 15 depends on claim 14, which in turn depends on claim 13 and claim 1. Claim 15 requires that the VEGF receptor fusion protein used in the methods described in Claim 14 is “aflibercept.” EX1001 at claim 15.

227. A POSA would have understood that at least the AU Eylea® Label and Vitti teach the limitations of claims 14 and 15 for at least the same reasons that they teach claims 12 and 13. Specifically, a POSA would have understood that the AU Eylea® Label disclosed that aflibercept is indicated in adults for the treatment of wet AMD. EX1009 at 24. And a POSA would further have understood that Vitti disclosed that aflibercept is the “standard of care treatment for neovascular AMD” and defined “AMD” as encompassing “wet AMD.” EX1007 at [0006], [0056].

7. Claims 16, 17

228. Claim 16 depends on claim 13, which in turn depends on claim 1. Claim 16 requires that the angiogenic eye disorder to be treated by the methods described in Claim 13 is “**diabetic macular edema.**” EX1001 at claim 16. Claim 17 depends on claim 16, which in turn depends on claim 13 and claim 1. Claim 17 requires that the VEGF receptor fusion protein is “**aflibercept.**” EX1001 at claim 17.

229. A POSA would have understood that at least the AU Eylea® Label and Vitti teach the limitations of claims 16 and 17 for at least the same reasons that they teach claims 12 and 13. Specifically, a POSA would have understood that the

AU Eylea® label disclosed that aflibercept is indicated in adults for the treatment of “diabetic macular oedema (DME).” EX1009 at 24. For the avoidance of doubt, a POSA would have understood that diabetic macular *oedema* and diabetic macular *edema* are alternative spellings of the same disorder. A POSA would have further understood that Vitti disclosed that aflibercept is the “standard of care treatment for . . . DME.” EX1007 at [0006].

8. Claims 18, 19

230. Claim 18 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**diabetic retinopathy**” (DR). EX1001 at claim 18. Claim 19 depends on claim 18, which in turn depends on claim 13 and claim 1, and requires that the VEGF receptor fusion protein is “**aflibercept**.” EX1001 at claim 19.

231. A POSA would have understood that at least the AU Eylea® label and Vitti teach the limitations of claims 18 and 19 for at least the reasons they teach claims 12 and 13.

232. The AU Eylea® Label teaches a POSA that aflibercept can be used to treat DR because aflibercept is indicated to treat DME. EX1009 at 24. Further, a

POSA would be aware that “DME is a manifestation of DR” and “is a major cause of the vision loss associated with diabetic retinopathy.” EX1016 at 2044.

233. A POSA would also know from the AU Eylea® Label that the VIVID and VISTA studies show that aflibercept could be used to treat DR. These studies tested the efficacy and safety of two dosing regimens of aflibercept, administered intravitreally, as compared with macular laser photocoagulation for 100 weeks in patients with DME. EX1016 at 2044. The 100-week results which showed, “a significantly greater proportion of eyes treated with IAI [i.e., intravitreal aflibercept] experienced an improvement of ≥ 2 steps in the DRSS score compared with eyes treated with laser control, suggesting that IAI also may promote regression of the underlying diabetic retinopathy in addition to the treatment of DME.” EX1016 at 2050. Further, “[a]t week 52, 33.3% and 33.8% of 2Q4 patients, 27.7% and 29.1% of 2Q8 patients, and 7.5% and 14.3% of laser control patients... experienced an improvement in the severity of diabetic retinopathy, as measured by a ≥ 2 step improvement in the diabetic retinopathy severity scale (DRSS).” EX1009 at 21.

234. Additionally, a POSA would know from the VIVID and VISTA efficacy outcomes in Table 9 of the AU Eylea® label that aflibercept could be used

to treat different severities of DR such as proliferative DR and non-proliferative DR. EX1009 at 18-22. Based on the label, a POSA would understand that the Early Treatment Diabetic Retinopathy Study (EDTRS) scale and the Diabetic Retinopathy Severity Scale (DRSS) were used in VIVID and VISTA. EX1009 at 18-19. It was well-known in the art that these scales traced the severity of DR and detail the progression from non-proliferative to proliferative DR. Further, a POSA would know that the label references some data, though limited, from patients with “proliferative retinopathy.” EX1009 at 25. Therefore, a POSA would understand that aflibercept could be used to treat DR including proliferative and non-proliferative DR.

235. A POSA with knowledge of Vitti and AU Eylea® label would know that intravitreal aflibercept could be used to treat DR as required by claims 18 and 19.

9. Claims 20, 21

236. Claim 20 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**non-proliferative diabetic retinopathy.**” EX1001 at claim 20. Claim 21 depends on claim 20, which in turn

depends on claim 13, which depends on claim 1, and requires that the VEGF fusion protein is “**aflibercept**.” EX1001 at claim 21.

237. A POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including different severities of DR such as non-proliferative DR for the reasons I discuss in Sections XI.A and XII.A. In addition to the reasons I set forth in claims 12, 13, 18, and 19, a POSA would understand that non-proliferative DR is a less severe form of DR. To the extent the AU Eylea® Label and Fiedler provide disclosures indicating the treatment of more severe forms of DR, including proliferative DR or DR with DME, a POSA would understand aflibercept to be capable of treating the less severe non-proliferative DR.

10. Claims 22, 23

238. Claim 22 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**proliferative diabetic retinopathy**.” EX1001 at claim 22. Claim 23 depends on claim 22, which in turn depends on claim 13 and claim 1, and requires that the VEGF fusion protein is “**aflibercept**.” EX1001 at claim 23.

239. A POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including different severities of DR such as proliferative DR for the reasons I discuss in Sections XI.A and XII.A. In addition to the reasons I set forth in claims 12, 13, 18, and 19, a POSA would also understand references to aflibercept being capable of treating DR encompasses all forms of DR. EX1011 at [0028].

11. Claims 24, 25

240. Claim 24 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**macular edema following retinal vein occlusion.**” EX1001 at claim 24. Claim 25 depends on claim 24, which in turn depends on claim 13 and claim 1, and requires that the VEGF fusion protein is “**aflibercept.**” EX1001 at claim 25.

241. A POSA would have understood that at least the AU Eylea® Label and Vitti teach the limitations of claims 24 and 25 for at least the same reasons that they teach claims 13. Specifically, a POSA would have understood that the AU Eylea® Label disclosed that aflibercept is indicated in adults for the treatment of visual impairment due to macular oedema secondary to CRVO. EX1009 at 24.

Again, for the avoidance of doubt, a POSA would have understood that oedema and edema are alternative spellings.

12. Claim 26

242. Claim 26 depends on claim 13, which in turn depends on claim 1. Claim 26 requires that the VEGF protein is “**aflibercept.**” EX1001 at claim 26.

243. A POSA would have understood that at least the AU Eylea® Label and Vitti teach the limitations of claim 26 for at least the same reasons that they teach claims 12 and 13. Specifically, a POSA would have understood that the AU Eylea® Label disclosed that aflibercept is indicated in adults for the treatment of several angiogenic eye disorders including, for example, wet AMD. EX1009 at 24. A POSA would have further understood that Vitti disclosed that aflibercept is the “standard of care” treatment for several angiogenic disorders including, for example, wet AMD. EX1007 at [0006].

13. Claim 27

244. Claim 27 depends on claim 1 and narrows the protein concentration limitation of claim 1 to “**about 8 mg aflibercept.**” EX1001 at claim 27.

245. A POSA would have understood that, for at least the same reasons explained with respect to claim 1, the AU Eylea® Label and Vitti teach, or at the very least, render this limitation obvious in combination with Larson.

14. Claims 28, 29

246. Claims 28 and 29 depend on claim 27, which in turn depends on claim 1. EX1001 at claims 28, 29. Claim 28 requires that the disorder to be treated is “**wet age-related macular degeneration**” (wet AMD) and claim 29 requires that the disorder to be treated is “**diabetic macular edema**” (DME). EX1001 at claims 28, 29.

247. A POSA would have understood that at least the AU Eylea® Label and Vitti teach the limitations of claim 28 and claim 29 for at least the same reasons that they teach Claims, 13, 14, 16, and 27.

15. Claim 30

248. Claim 30 depends on claim 27, which in turn depends on claim 1, and requires that the disorder to be treated is “**diabetic retinopathy**.” EX1001 at claim 30.

249. A POSA would have understood that at least the AU Eylea® label and Vitti teach the limitations of claim 30 for at least the same reasons that they teach claim 27, claim 18, and claim 1.

16. Claim 31

250. Claim 31 depends on claim 1. EX1001 at claim 31. In comparison to claim 1, claim 31 narrows the injection volume limitation to “**about 70 microliters,**” the dose limitation to “**about 8 mg aflibercept,**” and the concentration limitation to “**about 114.3 mg/ml.**” EX1001 at claims 1, 31.

251. Regarding the dose limitation of “about 8 mg aflibercept,” a POSA would have understood that, for the same reasons explained with respect to claim 1 and claim 27, the AU Eylea® Label and Vitti teach the limitations of claim 31 or at least that the AU Eylea® Label and Vitti in combination with Larson render this limitation obvious.

252. Regarding the concentration limitation of “about 114.3 mg/ml,” a POSA would have understood that Vitti disclosed, or at least rendered obvious, this limitation. A POSA would further understand that Vitti teaches pharmaceutical formulations that may contain “ 5 ± 0.75 mg/mL to 100 ± 15 mg/mL” of aflibercept. EX1007 at [0087], [0094]. I understand from Dr. Falconer that a

POSA would read 100 ± 15 mg/mL as encompassing up to 115 mg/ml. EX1004, 172.

253. A POSA would know that physicians have a desire to decrease the treatment burden on patients associated with long-term frequent intravitreal injections. This means that higher concentrations are ideal so patients do not need to travel to the clinic as frequently. The industry has continued to shift towards high-concentration protein formulations for this reason.

254. Regarding the injection volume limitation of “about 70 microliters,” a POSA would have understood that this limitation is disclosed, or at minimum, rendered obvious by Vitti. I understand from Dr. Falconer that a POSA would be able to calculate the injection volume using the 8 mg dose described by the AU Eylea® Label and Vitti, and the concentration range from Vitti. EX1004, 175-177. A POSA would be able to determine that an injection volume of 70 microliters would have an aflibercept concentration of 114.3 mg/mL at a dose of 8 mg. EX1007 at ¶¶ [0094], [0108], [0127]; EX1004, 175-177. Further, a POSA would know that a 70-microliter injection volume is suitable for injection into the human eye because it is between 20 and 100 microliters. Finally, I understand from counsel that because Vitti teaches a volume of “upto [*sic*] 100 μ L,” and because

the claimed volume falls within Vitti's range, Vitti renders this limitation presumptively obvious.

17. Claims 32-34

255. Claims 32-34 depend from claim 31, which in turn depends on claim 1. EX1001 at claims 31-34. Claim 32 requires that the disorder to be treated is **“wet age-related macular degeneration”** (wet AMD), claim 33 requires that the disorder to be treated is DME, and claim 34 requires that the disorder to be treated is **“diabetic retinopathy”** (DR). EX1001 at claims 32-34.

256. A POSA would have understood that at least the AU Eylea® label and Vitti teach the limitations of claims 32-34 for at least the same reasons that they teach claim 31 and claim 13.

D. Independent Claim 35

257. Independent claim 35 recites: “A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject, about 70 microliters of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept and having a viscosity of about 5-15 cP at 20° C.” EX1001 at claim 35.

258. In my opinion, a POSA would have had a reasonable expectation of success of developing a method of treating angiogenic eye disorders according to claim 35 in light of the disclosures of Vitti, the AU Eylea® label, and Larson.

1. 35[A] A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject

259. In my opinion, a POSA would understand that both Vitti and the AU Eylea® label teach “[a] method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject” as described in claim limitation 1[A] above in Section XI.B.1.

2. 35[B] about 70 microliters of

260. In my opinion, a POSA would understand that both Vitti and the AU Eylea® label teach “about 70 microliters of...” as described in claim 31 above in Section XI.C.16.

3. 35[C] an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept

261. In my opinion, a POSA would understand that Vitti teaches “an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept” or renders it obvious described in claim 31 above.

262. I understand from Dr. Falconer that the range of aflibercept in the liquid formulation disclosed by Vitti makes obvious the claimed range of “103-126 mg/ml.” EX1004, 185; EX1007 at [0094]. This is because a POSA would understand that Vitti teaches a “stable liquid pharmaceutical formulation” comprising the VEGF antagonist aflibercept and that the “liquid” formulation may be supplied “as an aqueous solution...for IVT [intravitreal] administration.” EX1007 at [0026], [0260]; EX1004, 184.

263. As I discuss above in several places, Vitti teaches formulations comprising a VEGF antagonist with a concentration of “ 10 ± 1.5 mg/mL to 100 ± 15.0 mg/mL”. EX1007 at [0087], [0094]. As I discuss above in Section XI.A, a POSA would have sought to have a high concentration, on the upper end of what is disclosed in Vitti. As described in claim 31, I understand from counsel that because the 85 to 115 mg/mL range from Vitti overlaps with the claimed range of “103-126 mg/ml,” this limitation is presumptively obvious.

264. I understand from Dr. Falconer that it would have been obvious for a POSA to have formulated high-concentration aflibercept in the range of about 103 to 126 mg/ml. EX1004, 185. As I discussed above, Vitti teaches high-concentration aqueous pharmaceutical formulations that contain 85 mg/mL to 115

mg/mL of aflibercept, which includes the range of 103 mg/mL to 115 mg/mL.

EX1007 at [0094]. According to Dr. Falconer, Vitti's teaching that its formulations containing up to 115 mg/mL of aflibercept "typically exhibit high levels of stability" and may be administered intravitreally, EX1007 at [0108], [0127], confirms that a skilled formulator would have reasonably expected to succeed in making a stable aflibercept formulation for intravitreal administration with a concentration of up to 115 mg/mL and within the claimed range. EX1004, 184.

4. 35[D] and having a viscosity of about 5-15 cP at 20° C

265. In my opinion, a POSA would understand that Larson teaches "and having a viscosity of about 5-15 cP at 20° C" as described in claim limitation 1[F] and claim 31 above.

E. Dependent Claims 36-38

266. Claims 36-38 depend from claim 35 and recite various angiogenic eye disorders. EX1001 at claim 36-38. Claim 36 requires "wet age-related macular degeneration," claim 37 requires "diabetic macular edema," and claim 38 requires "diabetic retinopathy." EX1001 at claim 36-38.

267. A POSA would have understood that at least the AU Eylea® label and Vitti teach the limitations of claims 36-38 for at least the same reasons that they teach claims 13, 16, 18, and 28-30.

XII. GROUND 2: Claims 1 and 4-38 are obvious over the Combination of Regeneron's Prior Art (Furfine, Dix, AU Eylea® Label), Fiedler, and Larson

268. In my opinion, a POSA would have found methods for treating an angiogenic eye disorder using a high concentration and a high dose of a VEGF receptor fusion protein as recited in claims 1 and 4-38 of the '036 patent obvious before May 2018. Specifically, a POSA would have been motivated to combine Regeneron's Prior Art Disclosures (Furfine, Dix, the AU Eylea® Label), Fiedler, and Larson to alleviate the treatment burden associated with repeat intravitreal injections by developing methods of treating angiogenic eye disorders with high concentrations (at least 100 mg/ml) of a VEGF antagonist (including aflibercept) that would allow for administration of a high dose (at least about 8 mg). And a POSA would have had a reasonable expectation of success in doing so in light of the combined teachings of Regeneron's Prior Art Disclosures (Furfine, Dix, the AU Eylea® Label), Fiedler, and Larson, which together teach and/or make obvious each and every limitation of claims 1 and 4-38.

A. A POSA Would Have Been Motivated to Combine Furfine, Dix, Fiedler, the AU Eylea® Label, and Larson with a Reasonable Expectation of Success

269. The combination of Furfine, Dix, Fiedler, the AU Eylea® Label, and Larson taught a POSA high concentration formulations of aflibercept allowing for high doses of aflibercept for treating angiogenic eye disorders prior to May 2018.

270. As I discuss in detail above in Section XI, which I incorporate by reference here, a POSA would have been motivated to develop high concentration formulations given the desire to target a high doses of aflibercept for treating these angiogenic eye disorders. It was well known in the art that frequent intravitreal injection of anti-VEGF proteins were burdensome for patients. It was also well known that high doses of anti-VEGF proteins could result in less frequent injections for patients which was desired. Indeed, there were teachings in the art for both aflibercept (Eylea®) and ranibizumab (Lucentis®) that demonstrated that higher doses were well tolerated and resulted in fewer injections. EX1034; EX1035; EX1026. And these studies were consistent with Regeneron's prior disclosure to the public that the maximum tolerated dose of aflibercept was not yet reached at 4 mg. EX1030 at 18. These examples encouraged a POSA to continue

searching for higher concentration formulations to make higher doses feasible for intravitreal administration.

271. Regeneron had already disclosed 8 mg of aflibercept to the public in the AU Eylea® Label. Not only did it disclose the use of 8 mg of aflibercept in clinical study to treat angiogenic eye disorders, but Regeneron found that it was tolerated and any concerns with overdosage were due the high volume of aflibercept administered and resulting increased intra ocular pressure as it was not a highly concentrated dose. EX1009 at 35. As I note above, this is consistent with toxicology data generated by Regeneron which found that drug-toxicity-related adverse events were only observed at exceedingly high doses when tested in monkeys. A POSA, thus, would have been motivated to target 8 mg of aflibercept in view of the AU Eylea® Label.

272. A POSA would have had a reasonable expectation of success in using an 8 mg dose to treat angiogenic eye disorders, like AMD, DME, and DR, given Regeneron's disclosures that the maximum tolerated dose had not yet been achieved after dosing patients with 4 mg, that higher doses were safe, effective, and well tolerated per Nguyen 2009, and that 8 mg (doubling the 4 mg dose in Nguyen) was generally well tolerated per the AU Eylea® Label. EX1034;

EX1030. A POSA would have further believed an 8 mg dose of aflibercept would be capable of treating patients with AMD, DME, and DR given the clinical trial disclosures in the AU Eylea® Label, and in view of the mechanism of action of aflibercept and knowledge in the art about the increased durability of anti-VEGF drugs with increased dose. EX1009 at 2-3, 18-22, 24; EX1039 at 1182. A POSA would thus have expected a high dose of a high concentration aflibercept formulation to be at least as efficacious for treating angiogenic eye disorders, including AMD, DME, and DR, as low dose Eylea®.

273. To develop an 8 mg dose of aflibercept for intravitreal injection, a POSA working with a formulator would have recognized the need to increase the concentration of aflibercept while balancing the amount of liquid a clinician could administer into a patient's eye.

274. The POSA would have been aware of numerous Regeneron prior art disclosures teaching stable ophthalmic formulations of high concentration aflibercept. For example, Furfine taught stable ophthalmic formulations with aflibercept concentrations up to 100 mg/mL that were suitable for intravitreal administration. EX1005 at 6:27-32. In Dix, Regeneron similarly disclosed, exemplified, and claimed stable formulations of 100 mg/ml of aflibercept for

intravenous and subcutaneous administration. EX1006 at 10:60-11:1, 19:37-42 (claim 1), 20:37-41 (claim 2). And Regeneron was not alone. Others in the art similarly described aflibercept concentrations of up to 100 mg/mL, including as disclosed in Fiedler. EX1011 at [0019], [0029], claim 4.

275. POSA would have desired the volume of a high concentration aflibercept formulation for intravitreal administration to be less than 100 uL to reduce the risk of unsafe increases in intraocular pressure resulting in permanent vision loss. *See* EX1015; EX1014. A POSA would have been motivated to combine the AU Eylea® Label with the teachings of Regeneron's high concentration art (i.e. Furfine and Dix) and the teachings of Fiedler, which further instructs a POSA that a high concentration formulation of aflibercept should have an injection volume below 100 uL—and preferably of a volume between 30 uL to 100 uL—to treat ocular diseases such as AMD, DME and DR. EX1011 at [0028], [0029].

276. While it was well known to clinicians that 100 uL was generally the upper safe limit for injection volume when intravitreally administering a drug to the eye given volume impacts on intraocular pressure as explained above in Section V.E.1, a POSA would have desired even lower volumes so as to limit

unsafe increases in ocular pressure for patients. For example, as I discuss above in Section V.D, it was known in the field that the volumes for low dose, 2 mg, Eylea® (aflibercept), Lucentis® (ranibizumab), and off-label Avastin® (bevacizumab) were all 50 uL. Knowing this, the POSA would have worked with a formulator to optimize the lowest injection volume for a high concentration, 8 mg dose of aflibercept.

277. I understand Dr. Falconer opines that a POSA would have been able to determine the range of possible concentrations for the aflibercept for the aqueous pharmaceutical formulation and that he provides a chart reflecting the resultant concentrations of aflibercept from injection volumes ranging from 50 uL to 100 uL. EX1004, 177. I understand Dr. Falconer further opines that the clinical considerations I discuss above regarding treatment burden would need to be balanced in view of competing consideration associated with formulating high-concentration protein formulations, including issues such as physical stability and viscosity. EX1004, Said differently from a clinician's perspective, if the concentration is too high, the liquid would be too thick (or viscous) for intravitreal injection to a patient.

278. Understanding those constraints, the POSA, relying on the formulator, would have sought out teachings in the art about administering high concentration proteins, like aflibercept, while keeping the viscosity low. A POSA would have been informed by the broad teachings in Larson of a target viscosity for injecting high-concentration protein formulations through the small needles required for intravitreal administration. Larson taught a way “to provide low-viscosity liquid formulations of pharmaceutically important proteins, especially high-molecular-weight proteins, such as mAbs,” that can “improve injectability and/or patient compliance, convenience, and comfort.” EX1010 at [0016]-[0018]. These high-concentration, low-viscosity liquid formulations have protein concentrations “between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL.” EX1010 at [0022]. A POSA would have understood from Larson that such formulations are administered with small needle gauges making them appropriate for intravitreal use. EX1010 at [0224], [0234]. Specifically, Larson taught that “[p]referred needle gauges for the delivery of the low-viscosity formulations include 27, 29, and 31 gauge, optionally thin walled.” EX1010 at [0079]. These needle sizes are consistent with those disclosed in the AU Eylea® Label, thus motivating a POSA to apply Larson’s viscosity teachings.

279. Larson taught preferred viscosities for administering high-concentration proteins, describing a most preferable viscosity of “less than or about 10 cP, when measured at 25° C.” EX1010 at [0075], [0077]. Larson teaches this preferred viscosity for a wide variety of proteins, including known anti-VEGF drugs, Eylea® and ranibizumab, further encouraging the POSA to view the preferred viscosities in Larson as applicable for intravitreal use (i.e., 30-gauge needles) of high concentrations. EX1010 at [0089], [0158], [0161], [0167].

280. A POSA would have had a reasonable expectation of success in achieving a viscosity range as described in Larson for the pharmaceutical formulations disclosed in the Regeneron prior art (Furfine, Dix, and the AU Eylea® Label) and Fiedler because Larson expressly teaches the desired viscosity range for protein concentrations of the levels taught in AU Eylea® Label so that they can be administered in a 30 gauge needle, necessary for intravitreal administration. Specifically, Larson disclosed that the “most preferably” have a viscosity of “less than or about 10 cP, when measured at 25°C” that could be administered using “a very small gauge needle, for example, between 27 and 31 gauge, typically 27, 29, or 31 gauge.” EX1010 at [0075], [0231].

281. Based on the above teachings in the art, in my opinion, a POSA would have had a motivation to combine the Regeneron Prior Disclosures (Furfine, Dix, and the AU Eylea® Label), Fiedler, and Larson with a reasonable expectation of success of achieving method of treating angiogenic eye disorders utilizing the high dose, high concentration formulations claimed in claims 1-38 of the '036 patent.

B. Independent Claim 1

282. Independent claim 1 recites the following:

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

EX1001 at claim 1.

283. In my opinion, a POSA would have had a reasonable expectation of success of developing a method of treating angiogenic eye disorders according to claim 1 in light of Regeneron's Prior Disclosures, Fiedler, and Larson.

1. 1[A] A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject

284. In my opinion, a POSA would have understood that Furfine and the AU Eylea® Label taught “[a] method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject.”

285. A POSA would have understood that Furfine disclosed ophthalmic formulations of VEGF-specific fusion protein antagonists. EX1005 at 1:15-21, 52-59. A POSA would have further understood that Furfine disclosed that “[t]he invention further features ophthalmic formulations provided in a pre-filled syringe or vial, *particularly suitable for intravitreal administration.*” EX1005 at 4:65-67.

286. A POSA would have understood that the AU Eylea® Label disclosed treating wet AMD, DME (and DR), and visual impairment due to macular oedema secondary to central retinal vein occlusion—which, as I discuss above in Section V.C are all angiogenic eye disorders—in humans by intravitreally administering aflibercept into the eyes of patients. EX1009 at 29-30.

2. 1 [B] In a volume of about 100 microliters or less

287. In my opinion, a POSA would have understood that Furfine and the AU Eylea® Label, in combination with Fiedler, disclose, or at least render obvious, “a volume of about 100 microliters or less.”

288. For the reasons discussed above in Sections V.A, V.E.1, a POSA would have understood that the eye is a highly specialized and sensitive organ and that there is a need to limit the volume of intravitreal injections.

289. A POSA would have understood that Furfine disclosed that “[t]he invention further features ophthalmic formulations provided in a *pre-filled syringe* or vial, particularly suitable for intravitreal administration.” EX1005 at 4:65-67. Although Furfine did not disclose the volume of the pre-filled syringe, a POSA would have understood that an intravitreal injection volume “of about 100 microliters or less” was conventional for ophthalmic pharmaceutical formulations, as shown by Fiedler. EX1011 at [0029]; Section V.E.1.

290. A POSA reading Furfine’s disclosure of a “pre-filled syringe” “suitable for intravitreal administration” would have been motivated to look to Fiedler for guidance as to the injection volume because Fiedler also disclosed a

pre-filled syringe containing a liquid formulation of VEGF antagonist. EX1005 at 4:65-67; EX1011 at [0018], [0019].

291. A POSA would have understood that Fiedler disclosed that “[p]referably, a volume of 30 to 100 μ L of the [VEGF antagonist] liquid formulation is administered to the patient.” EX1011 at [0029]. I understand from Alvotech’s counsel that because Fiedler’s disclosure of “30 to 100 μ L” is fully within the broader claimed range of “about 100 microliters or less,” it renders the claimed range presumptively obvious.

292. A POSA would have also understood that Fiedler further disclosed that a most preferable injection volume “administered to the patient is 0.05 ml” which equates to 50 μ L. EX1011 at [0067]. And a POSA would have understood that Fiedler’s disclosure of a preferred injection volume of 50 microliters is the same the injection volume disclosed in the AU Eylea® Label. EX1011 at [0067]; EX1009 at 29, 32, 34-35. And as charted above in Section V.E.1, a POSA would have further understood that other intravitreal injections of VEGF antagonists (including ranibizumab and bevacizumab) used intravitreal injection volumes of 50 microliters.

293. In my opinion, a POSA seeking to formulate a high-dose pharmaceutical formulation of VEGF receptor fusion protein antagonist (like aflibercept) for intravitreal injection would have had a good reason for utilizing an injection volume of 100 microliters or less (as disclosed in Fiedler) with a reasonable expectation of success.

3. 1[C] At least about 8 mg

294. In my opinion, a POSA would have understood that the AU Eylea® Label, Furfine, and Dix all disclosed, or at least rendered obvious, “at least about 8 mg of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component.”

295. A POSA would have understood that the AU Eylea® Label teaches an “8 mg” dose. EX1009 at 35. Specifically, a POSA would have understood that in Eylea® clinical trials, some patients received 8 mg doses, which were “generally well tolerated.” EX1009 at 35. A POSA would further understand that nothing in the AU Eylea® Label disclosed or suggested that the 8 mg of aflibercept was not efficacious or posed other concerns for patients. EX1009 at 35. While the AU Eylea® Label called these 8 mg doses “overdoses” (as the indicated treatment was

2 mg), the label does not suggest the 8 mg dose itself caused any concerns with efficacy or safety. A POSA would understand the only concern it identifies is increased interocular pressure from the “increased injection volume” associated with quadrupling the 2 mg dose (at 50 microliters) to 8 mg (which would be a volume of 200 microliters).

296. A POSA would further have understood that Furfine and Dix (like Vitti discussed above with respect to Ground 1) disclosed embodiments comprising “80 mg/ml”) of VEGF antagonist. EX1005 at 3:33-36; EX1006 at 3:44-46. Specifically, a POSA would have understood that Furfine disclosed a VEGF concentration of “or about 80 mg/ml.” EX1005 at 3:33-36. And a POSA would also have understood that Dix disclosed “a 40 mg/ml pre-lyophilized solution is lyophilized and reconstituted to an **80 mg/ml solution**”. EX1006 at 3:44-46. In my opinion, a POSA would have employed basic and routine mathematics, as described above in Section XI.B.3, to calculate the amount (in mg) of VEGF antagonists disclosed in Furfine and Dix. Accordingly, a POSA would have understood that an 80 mg/ml VEGF antagonist in a volume of 100 µl equals an 8 mg dose of VEGF antagonist ($80 \text{ mg/ml} \times 0.1 \text{ ml} = 8 \text{ mg}$). Section XI.B.3.

297. In my opinion, a POSA would have been motivated to treat a patient with a high dose of VEGF antagonist (resulting from the higher concentration), including “at least 8 mg,” with a reasonable expectation of success. Further, in my opinion, as explained above in Section XI.B.3, a POSA would have had a good reason to go from low-concentration (and correspondingly low-dose) VEGF antagonist formulations to high-concentration (and correspondingly high-dose) VEGF antagonist formulations and would have reasonably expected those formulations to treat the same angiogenic eye disorders as low-concentration (low-dose) VEGF antagonist in a safe and effective manner.

4. 1 [D] a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component

298. In my opinion, a POSA would have understood that Furfine, Dix, the AU Eylea® Label, and Larson disclosed this limitation because they are all directed to pharmaceutical formulations comprising a VEGF antagonist as recited in claim 1[D].

299. Furfine and Dix similarly teach a POSA an ophthalmic formulation comprising a VEGF “trap” antagonist described as “consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a

second VEGF receptor, and a multimerizing component.” EX1005 at 1:52-63; EX1006 at 1:56-62.

300. As I discuss above in Section XI.B.4, a POSA would have further understood that the AU Eylea® Label disclosed the structure of a VEGF trap (aflibercept) and its amino acid sequence. EX1009 at 1-2.

301. A POSA would have further understood that Larson that it describes a number of fusion proteins and disclosed that “EYLEA (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fe portion of human IgG1.” EX1010 at [0164], [0167].

302. The disclosures in Furfine, Dix, the AU Eylea® Label, and Larson are all consistent with how Regeneron characterized aflibercept to the patent office. Specifically, Regeneron stated “[t]he name of the approved product is EYLEA™. The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2}. Aflibercept is a fusion protein consisting of (a) a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Flt1 and an Ig domain 3 of a

second VEGF receptor that is human Flk1; and (b) an Fc portion of human IgG1.”
EX1013 at 2.

303. In my opinion, a POSA would have recognized that the above descriptions in Furfine, Dix, and the AU Eylea® Label each describe the same VEGF antagonist meeting this limitation. EX1005 at 1:52-63; EX1006 at 1:56-62; EX1009 at 1-2.

5. 1 [E] wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/mL of the VEGF receptor fusion protein

304. In my opinion, a POSA would have understood that Furfine, Dix, and the AU Eylea® Label disclosed this limitation.

305. Specifically, a POSA would have understood that Furfine disclosed a pharmaceutical formulation of 1-100 mg/ml VEGF-specific fusion protein antagonist. EX1005 at 2:4-6, 19:31-34 (claim 1).

306. A POSA would have also understood that Dix disclosed a “high concentration” pharmaceutical formulation comprising 50-100 mg/ml VEGF antagonist. EX1006 at 2:12-15. A POSA would have further understood that Dix provides specific examples of a formulation comprising 100 mg/ml VEGF antagonist. EX1006 at 10:60-11:1.

307. Specifically, a POSA would have understood that in Example 4, Dix tested the stability of a formulation with 100 mg/ml VEGF trap. EX1006 at 9:64-10:8. A POSA would have further understood that Example 4 of Dix tested the stability of a formulation with 100 mg/ml VEGF trap. EX1006 at 9:64-10:8. A POSA would have further understood that the pre-lyophilized formulation of Example 4 of Dix comprised VEGF trap at a protein concentration of 50 mg/ml. EX1006 at 10:44-47. A POSA would have further understood that Example 4 of Dix disclosed that following lyophilization (freeze-drying), the formulation was reconstituted to a liquid form. EX1006 at 10:1-6, 35-36 (Table 7 listing two 100 mg/ml formulations under “Liquid Formulations” heading). A POSA would have further understood that Example 4 of Dix disclosed that the reconstituted formulation comprised VEGF trap at a protein concentration of 100 mg/ml. EX1006 at 10:4-6.

308. Likewise, a POSA would have understood that in Example 5, Dix tested the stability and activity of a formulation having 100 mg/ml VEGF trap. EX1006 at 10:4-6. A POSA would have further understood that the pre-lyophilized formulation of Example 5 comprised VEGF trap at a protein concentration of 50 mg/ml. EX1006 at 10:65. A POSA would have further

understood that following lyophilization (freeze-drying), the formulation of Example 5 of Dix was reconstituted to a liquid form. EX1006 at 10:60, 66. A POSA would have further understood that the reconstituted formulation of Example 5 of Dix comprised VEGF trap at a protein concentration of 100 mg/ml. EX1006 at 11:1.

309. A POSA would have further understood that Dix provides specific examples of a formulation comprising 100 mg/ml VEGF antagonist. EX1006 at 19:37-42 (claim 1), 20:37-41 (claim 2). A POSA would have understood that claim 1 of Dix recites a “stable liquid formulation comprising 100 mg/mL of a VEGF antagonist.” EX1006 at 19:37-42. A POSA would have understood that claim 2 recites the “stable liquid formulation of claim 1 consisting of 100 mg/mL of the VEGF antagonist.” EX1006 at 20:37-41.

6. 1[F] and having a viscosity of about 5-15 centiPoise (cP) at 20°C

310. In my opinion, a POSA would have understood that Furfine and Dix in light of Larson disclosed this limitation. Specifically, a POSA would have understood that both Furfine and Dix (like Vitti discussed above) disclosed that excipients may be added to the disclosed pharmaceutical formulations “to provide a desired consistency or stabilizing effect.” EX1006 at 4:45-47. A POSA would

have recognized that viscosity contributes to the overall consistency of a liquid formulation, and a liquid with higher viscosity generally has a thicker consistency. EX1004, 48.

311. Because neither Furfine nor Dix specify a desired viscosity, a POSA would have been motivated to look to other references to determine the desired viscosity. As explained above in Section XI.B.6, a POSA would have looked to Larson because Larson disclosed the viscosity of high-concentration biologics must be low enough that the biologic can be administered intravitreally through a 18-32 gauge needle—which encompasses the 30-gauge needle taught in the Label. EX1010 at ¶49.

312. Given this, in my opinion, it would have been obvious to a POSA to implement Larson’s disclosed viscosity range (i.e., “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.”) in the formulations taught in at least Furfine and Dix, for the same reasons discussed above in Sections XI.B.6, XII.A. I understand from Dr. Falconer that this viscosity range would have had a reasonable expectation of success for the same reasons discussed above in Section XI.B.6, XII.A. I further understand from Dr. Falconer that there were several strategies to improve the viscosity characteristics of high-

concentration biologics and that with a reasonable expectation of success any one of a number of these available solutions could have been applied to an aqueous pharmaceutical formulation containing at least 100 mg/mL of aflibercept, as taught in Furfine and Dix, to achieve a viscosity of about 5-15 cP at 20° C, as taught in Larson. EX1004, 198.

C. Dependent Claims 4-34

1. Claims 4-8

313. Each of claims 4-8 depend on claim 1 and recite various viscosities at 20° C for the formulations described in the method of claim 1. EX1001 at claims 4-8. Specifically, claim 4 recites “**about 10-13 cP,**” claim 5 recites “**about 11-12 cP,**” claim 6 recites “**about 12-15 cP,**” claim 7 recites “**about 5 cP,**” and claim 8 recites “**about 6 cP.**” EX1001 at claims 4-8.

314. I understand from Dr. Falconer that a POSA would know to apply the viscosity teachings of Larson to the 100 mg/mL aflibercept formulations taught in Furfine, Dix, and Fiedler to achieve a viscosity of 5-15 cP at 20° C. EX1004, 198; EX1005 at 2:4-9; EX1006 at 10:29-32; EX1011 at [0019]. A POSA would look to Larson which teaches desired viscosities for high concentration proteins,

particularly “preferably less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C.” EX1010 at [0075], [0077].

315. For the same reasons I understand from Dr. Falconer and discuss above in Section XI.C.1 with respect to GROUND 1, a POSA would have understood that high concentration protein formulations, such as those described in Furfine, Dix, Fiedler, and Larson, that had a viscosity of less than 20 cP at 25° C would have a viscosity of less than about 22.52 cP at 20° C. And such formulations with a viscosity of less than 10 cP at 25° C would have a viscosity of less than about 11.26 cP at 20° C.

316. Therefore, in my opinion, a POSA would understand with the aid of a formulator that Larson discloses viscosities at 20° C of “about 10-13 cP” recited by claim 4, “about 11-12 cP” recited by claim 5, “about 12-15 cP” recited by claim 6, “about 5 cP” recited by claim 7, and “about 6 cP” recited by claim 8. EX1001 at claims 4-8.

2. Claims 9, 10

317. Claims 9 and 10 depend on claim 1. EX1001 at claims 9, 10. Specifically, claim 9 requires the formulation described in the method of claim 1 **“comprises a sugar.”** EX1001 at claim 9. And claim 10 requires the formulation

described in the method of claim 1 “**comprises sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol.**” EX1001 at claim 10.

318. A POSA working with a formulator would have further understood that Furfine discloses ophthalmic formulations optionally comprising a stabilizing agent that may be sucrose, which I understand from Dr. Falconer. EX1005 at 2:15-16; EX1004, 281. Similarly, Dix also taught a POSA the use of sucrose. EX1004, 218; EX1006 at 10:1-11:1. Dix states, for example, that “[i]n one embodiment, the thermal stabilizers are NaCl and/or sucrose.” EX1006 at 2:2-3.

319. I understand from counsel that because claim 10 recites specific sugars in the alternative, the disclosure of sucrose is sufficient to disclose a “formulation compris[ing] sucrose, trehalose, sorbitol, mannitol, propane, sulfonic acid or glycerol.” EX1001 at claim 10.

3. Claim 11

320. Claim 11 depends on claim 1. Claim 11 specifically requires that the formulation described in the method of claim 1 “**comprises an amino acid.**” EX1001 at claim 11.

321. A POSA reading Dix would understand that it teaches stable formulations comprising a VEGF-specific fusion protein antagonist that include histidine, an amino acid. EX1006 at 10:14-11:1, cls. 1-2.

4. Claim 12

322. Claim 12 depends on claim 1. Claim 12 requires that the VEGF receptor fusion protein described in the method of claim 1 is “**aflibercept.**” EX1001 at claim 12.

323. A POSA would have understood that Furfine, Dix, Fiedler, and the AU Eylea® Label each disclose a VEGF receptor fusion protein that is aflibercept. The AU Eylea® Label states that “Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.” EX1009 at 2. Fiedler similarly teaches “[a]flibercept, marketed under the name Eylea®, is a recombinant fusion protein consisting of the VEGF receptors 1 and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin.” EX1011 at [0003].

324. While both Furfine and Dix do not expressly use the term “aflibercept,” a POSA would understand aflibercept is disclosed by the description of the VEGF-specific fusion protein antagonist. Both Furfine and Dix teach a

VEGF-specific fusion protein comprising “a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component. EX1005 at 1:58-64; EX1006 at 1:56-61. Both further characterize the fusion protein as a VEGF Trap, which a POSA would understand to be conveying aflibercept. EX1005 at 1:63-64; EX1006 at 1:35-40.

325. The disclosures in Furfine, Dix, the AU Eylea® Label, and Larson are all consistent with how Regeneron characterized aflibercept to the patent office. Specifically, Regeneron stated “[t]he name of the approved product is EYLEA™. The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2}. Aflibercept is a fusion protein consisting of (a) a vascular endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Flt1 and an Ig domain 3 of a second VEGF receptor that is human Flk1; and (b) an Fc portion of human IgG1.” EX1013 at 2.

5. Claim 13

326. Claim 13 depends on claim 1. Claim 13 requires that the angiogenic eye disorder described to be treated in the methods of claim 1 is one of the following disorders: **“age-related macular degeneration (wet), macular edema, macular edema following retinal vein occlusion, retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DMA), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathy, non-proliferative diabetic retinopathy, and/or proliferative diabetic retinopathy.”** EX1001 at claim 13.

327. A POSA would have understood the use of aflibercept for treating angiogenic eye disorders was well known as of May 2018. EX1009 at 21. For instance, a POSA would have understood that the AU Eylea® Label discloses that aflibercept is indicated in adults for the treatment of wet AMD, CRVO, and DME (a manifestation of DR). EX1009 at 21.

328. I understand from counsel that the use of the disjunctive “and/or” in claim 13 creates alternative subsets of claim coverage. Accordingly, I understand that the AU Eylea® Label’s disclosure of treating wet AMD with aflibercept satisfies the requirements of claim 13.

329. Further, a POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including AMD, DME, and DR for the reasons I discuss in Sections XI.A and XII.A. Fiedler further supports this expectation as it describes up to an intravitreal administration of 100 mg/ml aflibercept formulation, in a pre-filled syringe that can be used for patients have ocular diseases including “age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME)”, and “diabetic retinopathy in patients with diabetic macular edema.” EX1011 at [0018], [0019], [0028].

6. Claims 14, 15

330. Claim 14 depends on claim 13, which in turn depends on claim 1. Claim 14 requires that the angiogenic eye disorder treated using the methods of claims 1 and 13 is “**wet age-related macular degeneration**,” also known as wet AMD. EX1001 at claim 14. Claim 15 depends on claim 14, which in turn depends

on claim 13 and claim 1. Claim 15 requires that the VEGF receptor fusion protein used in the methods described in Claim 14 is “**aflibercept**.” EX1001 at claim 15.

331. A POSA would have understood that at least the AU Eylea® Label, and Fiedler teach the limitations of claims 14 and 15 for at least the same reasons that they teach claims 12 and 13.

332. A POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including AMD for the reasons I discuss in Sections XI.A and XII.A. A POSA would have understood that the AU Eylea® Label disclosed that aflibercept is indicated in adults for the treatment of wet AMD. EX1009 at 24. And a POSA would further have understood that Fiedler to disclose intravitreal administration of 100 mg/ml aflibercept formulation, in a pre-filled syringe that can be used for treating patients with “age-related macular degeneration (AMD).” EX1011 at [0018], [0019], [0028].

7. Claims 16, 17

333. Claim 16 depends on claim 13, which in turn depends on claim 1. Claim 16 requires that the angiogenic eye disorder to be treated by the methods described in Claim 13 is “**diabetic macular edema**.” EX1001 at claim 16. Claim

17 depends on claim 16, which in turn depends on claim 13 and claim 1. Claim 17 requires that the VEGF receptor fusion protein is “**aflibercept**.” EX1001 at claim 17.

334. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the limitations of claims 16 and 17 for at least the same reasons that they teach claims 12 and 13.

335. A POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including DME for the reasons I discuss in Sections XI.A and XII.A. A POSA would have understood that the AU Eylea® Label disclosed that aflibercept is indicated in adults for the treatment of “diabetic macular oedema (DME).” EX1009 at 24. For the avoidance of doubt, a POSA would have understood that diabetic macular *o*edema and diabetic macular *e*dema are alternative spellings of the same disorder. And a POSA would further have understood that Fiedler to disclose intravitreal administration of 100 mg/ml aflibercept formulation, in a pre-filled syringe that can be used for treating patients with “visual impairment due to diabetic macular oedema (DME).” EX1011 at [0018], [0019], [0028]. As I

discuss above, a POSA would have understood that diabetic macular *o*edema and diabetic macular *e*dema are alternative spellings of the same disorder.

8. Claims 18, 19

336. Claim 18 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**diabetic retinopathy**” (DR). EX1001 at claim 18. Claim 19 depends on claim 18, which in turn depends on claim 13 and claim 1, and requires that the VEGF receptor fusion protein is “**aflibercept**.” EX1001 at claim 19.

337. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the limitations of claims 18 and 19 for at least the reasons they teach claims 12 and 13.

338. Further, a POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including DR for the reasons I discuss in Sections XI.A and XII.A. The AU Eylea® Label teaches a POSA, that aflibercept can be used to treat DR based on the clinical data from the VIVID and VISTA trials for DME. EX1009 at 18-22. Further, a POSA would be aware that “DME is a manifestation of DR” and “is a

major cause of the vision loss associated with diabetic retinopathy.” EX1016 at 2044.

339. For the same reasons that I discuss above in Section XI.C.8 regarding GROUND 1, a POSA would also know from the discussion of the VIVID and VISTA studies in the AU Eylea® Label that aflibercept could be used to treat DR, including different severities of DR.

340. A POSA would further have understood that Fiedler to disclose intravitreal administration of 100 mg/ml aflibercept formulation, in a pre-filled syringe that can be used for treating “diabetic retinopathy in patients with diabetic macular edema.” EX1011 at [0018], [0019], [0028].

9. Claims 20, 21

341. Claim 20 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**non-proliferative diabetic retinopathy**.” EX1001 at claim 20. Claim 21 depends on claim 20, which in turn depends on claim 13, which depends on claim 1, and requires that the VEGF fusion protein is “**aflibercept**.” EX1001 at claim 21.

342. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the limitations of claims 20 and 21 for at least the same reasons that they teach claims 12, 13, 18, and 19.

343. A POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including different severities of DR such as non-proliferative DR for the reasons I discuss in Sections XI.A and XII.A. In addition to the reasons I set forth in claims 12, 13, 18, and 19, a POSA would understand that non-proliferative DR is a less severe form of DR. To the extent the AU Eylea® Label and Fiedler provide disclosures indicating the treatment of more severe forms of DR, including proliferative DR or DR with DME, a POSA would understand aflibercept to be capable of treating the less severe non-proliferative DR.

10. Claims 22, 23

344. Claim 22 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**proliferative diabetic retinopathy.**” EX1001 at claim 22. Claim 23 depends on claim 22, which in turn depends on claim 13 and claim 1, and requires that the VEGF fusion protein is “**aflibercept.**” EX1001 at claim 23.

345. In addition to the reasons I set forth in claims 12, 13, 18, and 19, a POSA would also understand references to aflibercept being capable of treating DR encompasses all forms of DR. EX1011 at [0028].

11. Claims 24, 25

346. Claim 24 depends on claim 13, which in turn depends on claim 1, and requires that the disorder to be treated is “**macular edema following retinal vein occlusion.**” EX1001 at claim 24. Claim 25 depends on claim 24, which in turn depends on claim 13 and claim 1, and requires that the VEGF fusion protein is “**aflibercept.**” EX1001 at claim 25.

347. A POSA would have understood that at least the AU Eylea® Label teach the limitations of claims 24 and 25 for at least the same reasons that they teach claims 13. Specifically, a POSA would have understood that the AU Eylea® Label disclosed that aflibercept is indicated in adults for the treatment of visual impairment due to macular oedema secondary to CRVO. EX1009 at 24. Again, for the avoidance of doubt, a POSA would have understood that oedema and edema are alternative spellings.

12. Claim 26

348. Claim 26 depends on claim 13, which in turn depends on claim 1. Claim 26 requires that the VEGF protein is “**aflibercept.**” EX1001 at claim 26.

349. A POSA would have expected that high concentration, high dose aflibercept would treat the same angiogenic eye disorders as low-dose aflibercept including AMD for the reasons I discuss in Sections XI.A and XII.A. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the limitations of claim 26 for at least the same reasons that they teach claims 12 and 13. Specifically, a POSA would have understood that the AU Eylea® Label disclosed that aflibercept is indicated in adults for the treatment of several angiogenic eye disorders including, for example, wet AMD. EX1009, 24. A POSA would further have understood that Fiedler to disclose intravitreal administration of 100 mg/ml aflibercept formulation, in a pre-filled syringe that can be used for treating patients with “age-related macular degeneration (AMD).” EX1011 at [0018], [0019], [0028].

13. Claim 27

350. Claim 27 depends on claim 1 and narrows the protein concentration limitation of claim 1 to “**about 8 mg aflibercept.**” EX1001 at claim 27.

351. A POSA would have understood that, for at least the same reasons explained with respect to claim 1, at least the AU Eylea® Label taught the limitations of claim 27.

14. Claims 28, 29

352. Claims 28 and 29 depend on claim 27, which in turn depends on claim 1. EX1001 at claims 28, 29. Claim 28 requires that the disorder to be treated is “**wet age-related macular degeneration**” (wet AMD) and claim 29 requires that the disorder to be treated is “**diabetic macular edema**” (DME). EX1001 at claims 28, 29.

353. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the limitations of claim 28 and claim 29 for at least the same reasons that they teach Claims, 13, 14, 16, and 27.

15. Claim 30

354. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the limitations of claim 30 for at least the same reasons that they teach claim 27, claim 18, and claim 1.

16. Claim 31

355. Claim 31 depends on claim 1. EX1001 at claim 31. In comparison to claim 1, claim 31 narrows the injection volume limitation to “**about 70**

microliters,” the dose limitation to **“about 8 mg aflibercept,”** and the concentration limitation to **“about 114.3 mg/ml.”** EX1001 at claims 1, 31.

356. Regarding the dose limitation of “about 8 mg aflibercept,” a POSA would have understood that this limitation is taught, or at minimum obvious, by the AU Eylea® Label, Furfine, and Dix for at least the same reasons explained above with respect to claim 1 in Section XII.B.3.

357. Regarding the concentration limitation of “about 114.3 mg/ml,” a POSA would have understood that Furfine, Dix, and Fiedler disclose, or at least rendered obvious, this limitation for at least the same reasons explained above with respect to claim 1. In addition to those reason, I understand from, and rely on, Dr. Falconer’s opinions that a POSA would have been motivated and had a reasonable expectation of success of using a high concentration of 114.3 mg/ml aflibercept formulation suitable for intravitreal administration. EX1004, 242. As Dr. Falconer explains, there is only a 15% difference between 114.3 mg/ml as recited in claim 31 and the 100 mg/ml that was taught by Furfine, Dix, and Fiedler. EX1004, 244. He goes on to explain that this minor increase in concentration would not be expected to meaningfully affect the stability and viscosity properties of an aflibercept formulation and that a POSA would have known how to make

adjustments to arrive at a stable ophthalmic formulation suitable for intravitreal injection. EX1004, 244-245. Dr. Falconer described how this was confirmed by the state of the art, including by Vitti. EX1004, 245. As I discuss above in Section XI.C.16, and as similarly conveyed by Dr. Falconer, Vitti taught a POSA stable, liquid pharmaceutical formulations containing up to “100±15 mg/mL of a VEGF antagonist” that could be administered via a 30-gauge needle for intravitreal administration to patients with angiogenic disorders. EX1007 at [0094], [0108], [0115], [0127]; EX1004, 245.

358. As I discuss above in Section XII.B.3, the AU Eylea® Label teaches an aflibercept dose of at least about 8 mg. With respect to an injection volume appropriate for intravitreally administering an 8 mg dose, it was well known in the art that the injection volume for intravitreally administered formulations ranged from 50 µL to 100 µL. Section V.E.1 (discussing limits on intravitreal injection volume). This is consistent with Fiedler’s disclosure of an injection volume of “30 to 100 µL.” EX1004, ¶29. Indeed, 100 µL was, and still is, considered the known upper safe volume limit for a liquid formulation for intravitreal injection into the eye. Section V.E.1 (discussing limits on intravitreal injection volume). While a clinician would consider any injection volume between 50 µL and 100 µL to have

been clinically acceptable for intravitreal administration, the clinician would still much prefer a lower injection volume within that range due to the lower risk of adverse clinical events associated with increased intraocular pressure from higher-volume injections.

359. This clinical desire for low injection volume is exemplified by the injection volumes for anti-VEGF products in the prior art. For example, the AU Eylea® Label teaches low-concentration Eylea® (2 mg) was delivered in a 50µL volume. EX1009 at 35. This was also true for Lucentis® and Avastin®, as I discuss above in Section V.E.1. In my opinion, a clinician would prefer to deliver the 8mg dose of aflibercept in the same 50µL volume, or a volume as close to 50µL as possible, which would necessarily require a higher-concentration of aflibercept.

360. As I explain above in Sections XI.A and XII.A, the desire to decrease the treatment burden on patients associated with long-term, frequent intravitreal injections drove the field to move towards higher-concentration ophthalmic formulations that provided for higher doses for intravitreal administration. To achieve this goal, it would have been desirable from a clinical perspective to

increase the concentration of the 100 mg/mL aflibercept formulations taught in Furfine, Dix, and Fiedler.

361. I understand from Dr. Falconer that given an 8 mg and injection volume ranging from 50 μ L to 100 μ L a formulator consulting with a clinician would be able to determine the range of possible concentrations for the aflibercept in the aqueous pharmaceutical formulation is 80 mg/mL to 160 mg/mL. EX1004, 250. It is my understanding from Dr. Falconer that based on this range, a skilled formulator would have been able to identify, and reasonably expect to succeed in obtaining, a stable aqueous pharmaceutical formulation for intravitreal administration containing 114.3 mg/mL aflibercept as a matter of routine optimization. EX1004, 250.

362. I understand from Dr. Falconer that while it may have been possible to obtain an aflibercept formulation with a protein concentration above 115 mg/mL, a skilled formulator would have understood that higher-concentrations increased the risk of failure. EX1004, 251. He further informed me that higher-concentrations increase risk of aggregation, increased viscosity, and thus potentially require additional stabilizing and/or viscosity-reducing excipients, all of

which complicate the formulation and increase the risk of a failed formulation. EX1004, 251.

363. This then means that the clinical considerations related to patient treatment burden and adverse clinical events I discuss (which favor a higher protein concentration to deliver an 8 mg dose of aflibercept at a lower-volume), must be balanced with the competing formulation considerations related to aggregation and viscosity (which favor a lower protein concentration to deliver the same 8 mg dose at a higher volume) that Dr. Falconer describes. EX1004, 252. I further understand from Dr. Falconer that the formulator and clinician working together would have recognized that a formulation containing 114.3 mg/mL of aflibercept for providing an 8 mg dose at a volume of 70 μ L would have been a suitable option. EX1004, 252. I further understand a skilled formulator would have reasonably expected to successfully obtain formulation suitable for intravitreal injection at 114.3 mg/ml based on Furfine, Dix, and Fiedler as a matter of routine optimization. EX1004, 253. In my opinion, a POSA clinician would find the 70 μ L volume—slightly more than 50 μ L of prior treatments but less than 100 μ L—to be a reasonable volume to improve the patient experience and minimize potential adverse events. Finally, the claimed “about 70 microliter”

volume is within Fiedler's range of "30 to 100 μ L," and I understand from counsel that means the limitation is presumptively obvious. EX1004, ¶29.

17. Claims 32-34

364. Claims 32-34 depend from claim 31, which in turn depends on claim 1. EX1001 at claims 31-34. Claim 32 requires that the disorder to be treated is "**wet age-related macular degeneration**" (wet AMD), claim 33 requires that the disorder to be treated is DME, and claim 34 requires that the disorder to be treated is "**diabetic retinopathy**" (DR). EX1001 at claims 32-34.

365. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the limitations of claims 32-34 for at least the same reasons that they teach claim 31 and claim 13.

D. Independent Claim 35

1. 35[A] A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject

366. In my opinion, a POSA would understand that both Furfine and the AU Eylea® Label disclosed "[a] method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into an eye of the subject" as described in claim limitation 1[A] above in Section XII.B.1.

2. 35[B] about 70 microliters of

367. In my opinion, a POSA would understand that both Furfine and the AU Eylea® Label disclosed or at least render obvious the limitation of “about 70 microliters of...” as described in claim 31 above in Section XII.C.16.

3. 35[C] an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept

368. In my opinion, a POSA would understand that Furfine, Dix, the AU Eylea® Label in view of Larson disclosed or rendered obvious “an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept” as described in claim 31 above in Section XII.C.16.

369. As I discuss above, I understand from Dr. Falconer that after determining the range of possible concentrations for an aflibercept dose of 8 mg and an injection volume of 50 µL to 100 µL, a skilled formulator would have been able to identify, and reasonably expect to succeed in obtaining, a stable aqueous pharmaceutical formulation for intravitreal administration containing 115 mg/mL aflibercept as a matter of routine optimization. EX1004, 259. I understand from counsel that because a protein concentration of 114.3 mg/ml falls within the claimed range of 103-126 mg/ml, this limitation would be presumptively obvious as a matter of law.

4. 35[D] and having a viscosity of about 5-15 cP at 20° C

370. In my opinion, a POSA would understand that Furfine, Dix, and the AU Eylea® Label in view of Larson disclosed “and having a viscosity of about 5-15 cP at 20° C” as described in claim limitation 1[F] and claim 31 above in Sections XII.B.6 and XII.C.16, respectively.

E. Dependent Claims 36-38

371. Claims 36-38 depend from claim 35 and recite various angiogenic eye disorders. EX1001 at claim 36-38. Claim 36 requires “wet age-related macular degeneration,” claim 37 requires “diabetic macular edema,” and claim 38 requires “diabetic retinopathy.” EX1001 at claim 36-38.

372. A POSA would have understood that at least the AU Eylea® Label and Fiedler teach the specific angiogenic eye disorder limitations of claims 36-38 for at least the same reasons that they teach claims 13, 14, 16, 18, 28-30, and 32-34.

XIII. GROUND 4: THE COMBINATION OF VITTI, THE AU EYLEA® LABEL, LARSON, AND THE 2011 EYLEA® CLINICAL REVIEW DISCLOSE EACH AND EVERY LIMITATION OF CLAIMS 2 AND 3

373. Claims 2 and 3 depend from the methods of claim 1. Claim 2 requires that following intravitreal injection in accordance with the methods of Claim 1, “the subject maintains or achieves a reduction in central retinal thickness but does

not experience a significant increase in blood pressure.” EX1001 at 61:62-65.

Claim 3 similarly requires that “the subject maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure.” EX1001 at 61:66-62:52. In my opinion, claims 2 and 3 of the ’036 patent are obvious over the combination of Vitti, the AU Eylea® Label, Larson, and the 2011 Eylea® Clinical Review.

374. A POSA would have been motivated to combine Vitti, the AU Eylea® Label, and the Larson with a reasonable expectation of success for the reasons I discuss with respect to Claim 1 in Section XI.A, which I incorporate by reference here.

375. A POSA would have recognized that the AU Eylea® Label disclosed a low dose intravitreal administration of aflibercept that maintained or achieved both “**a reduction in central retinal thickness**” as required by claim 2. The AU Eylea® Label reports on various clinical trials for different angiogenic eye disorders, including AMD and DME/DR, that observed decreases in central retinal thickness. EX1009, 3. For example, with respect to AMD, the AU Eylea® Label states that “[i]n patients treated with EYLEA (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness

decreased soon after treatment initiation,” that “there were mean decrease in retinal thickness” observed in the Phase III VIEW 1 and VIEW 2 clinical studies, and that “reduction in retinal thickness were generally maintained in the second year of the studies.” EX1009, 3.

376. Regarding DME/DR, the AU Eylea® Label teaches that patients treated with Eylea® were observed to have a “rapid and robust response in morphology (central retinal thickness [CRT]) as assessed by OCT [] soon after treatment initiation” and that “[t]he mean change in CRT from baseline to week 52 was statistically significant favouring EYLEA and was maintained through week 100.” EX1009, 6.

377. A POSA would have recognized that the AU Eylea® Label disclosed a low dose intravitreal administration of aflibercept that maintained or achieved both “**maintains or achieves an improvement in best corrected visual acuity**” as required by claim 3. The clinical trials discussed in the AU Eylea® Label also teach a POSA that at least one subject maintained visual acuity under the Best Corrected Visual Acuity (BCVA) test. EX1009, 8-10. For example, the data from VIEW 1 and VIEW 2 evaluating aflibercept for AMD demonstrated that the vast majority of patients maintained visual acuity (<15 letters of BCVA loss) and

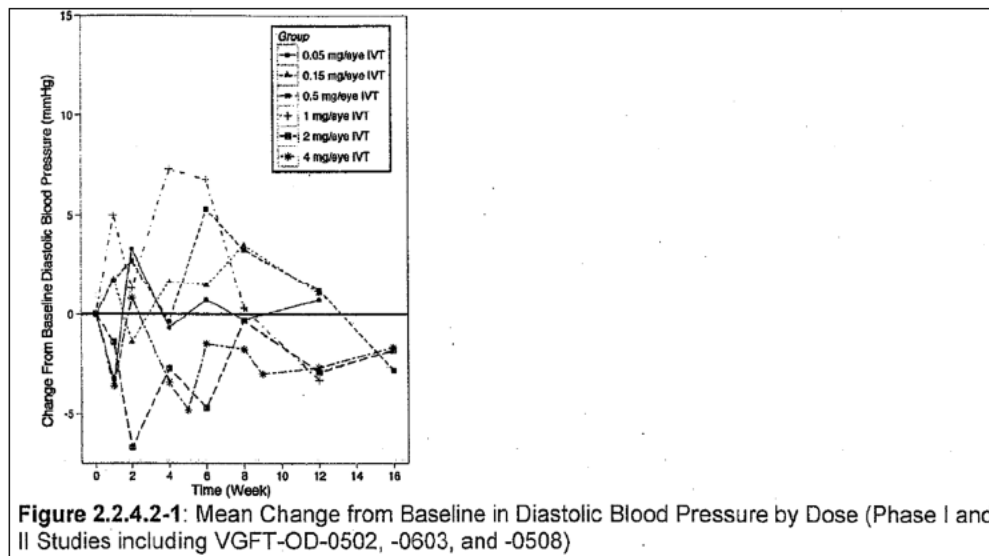
roughly a third a patients gained at least 15 letters of vision from baseline.

EX1009, 8-10, Table 3, Figure 3.

378. A POSA would have had a reasonable expectation of success of a high concentration, 8 mg dose of aflibercept would experience at least the same clinical effects—including a reduction in central retinal thickness and maintenance or improvement in BCVA— as a low concentration, low dose of aflibercept for the reasons I again discuss in Section XI.A.

379. For both Claims 2 and 3, a POSA would have sought to understand the effects of intravitreally administered aflibercept on blood pressure, and would have been motivated to consult available aflibercept clinical data, including that reported in the FDA’s 2011 Clinical Pharmacology and Biopharmaceutics Review. The 2011 Clinical Review posed several questions regarding the clinical pharmacology for aflibercept for which Regeneron provided responses. FDA asked: “What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.” EX1008 at 11. In response, Regeneron acknowledged the increased diastolic and systolic blood pressure were observed for systemic administration of aflibercept,

which a POSA would have understood to mean intravenous administration. In contrast, Regeneron observed that “[w]hen administered via the IVT [intravitreal] route, aflibercept was not observed to cause increases in DBP (Figure 2.2.4.2-1) or SBP.” EX1008 at 10. I have reproduced Figure 2.2.4.2-1 from page 11 of the 2011 Clinical Review below for ease of reference:



380. A POSA would have been further informed by the data comparing systemic exposure (Cmax) of free and bound aflibercept and data comparing blood pressure change in response to dose over time following intravenous and intravitreal administration, reported in Figures 2.2.4.2-2 and 2.2.4.2-3, respectively. EX1008 at 11-12.

381. The data in the 2011 Eylea® Clinical Review teaches a POSA that intravitreally administration of low dose aflibercept did not cause a significant increase in blood pressure. This is consistent with the lack of any information—including no data or warning— regarding blood pressure in the AU Eylea® Label.

382. A POSA would reasonably expect the lack of a significant increase in blood pressure after intravitreal administration of low dose Eylea® to also be the case for intravitreal injection of higher concentrations, 8 mg aflibercept (≥ 100 mg/ml) formulations taught by Vitti and the AU Eylea Label. EX1009 at 35 (“Overdosage”). As I discuss in Section XI.A, a POSA would have reasonably expected intravitreal injection of higher-concentration aflibercept to have at least the same clinical effect as low dose Eylea®.

383. In my opinion, a POSA would have been motivated to combine Vitti, the AU Eylea® Label, Larson, and the 2011 Eylea® Clinical Review with a reasonable expectation of success making Claims 2 and 3 of the '036 patent obvious.

XIV. GROUND 5: THE COMBINATION OF FURFINE, DIX, THE AU EYLEA® LABEL, FIEDLER, LARSON, AND THE 2011 EYLEA®

**CLINICAL REVIEW DISCLOSE EACH AND EVERY LIMITATION
OF CLAIMS 2 AND 3**

384. As discussed in Section XIII, claims 2 and 3 depend from the methods of claim 1. Claim 2 requires that following intravitreal injection in accordance with the methods of Claim 1, “the subject maintains or achieves a reduction in central retinal thickness but does not experience a significant increase in blood pressure.” EX1001 at 61:62-65. Claim 3 similarly requires that “the subject maintains or achieves an improvement in best corrected visual acuity but does not experience a significant increase in blood pressure.” EX1001 at 61:66-62:52. In my opinion, claims 2 and 3 of the ’036 patent are obvious over the combination of Larson, Vitti, the AU Eylea® Label, and the 2011 Eylea® Clinical Review.

385. A POSA would have been motivated to combine Furfine, Dix, the AU Eylea® Label, Fiedler and Larson with a reasonable expectation of success for the reasons I discuss with respect to Claim 1 in Section XII.A, which I incorporate by reference here.

386. A POSA would have recognized that the Eylea® 2015 Label disclosed a low dose intravitreal administration of aflibercept that maintained or achieved both “**a reduction in central retinal thickness**” as required by claim 2

and “**an improvement in best corrected visual acuity**” as required by claim 3 for the same reasons I discuss above in Section XIII with respect to GROUND 5.

387. A POSA would have had a reasonable expectation of success of a high concentration, 8 mg dose of aflibercept would experience at least the same clinical effects—including a reduction in central retinal thickness and maintenance or improvement in BCVA— as a low concentration, low dose of aflibercept for the reasons I again discuss in Sections XI.A and XII.A.

388. Like Claims 2 and 3, a POSA would have sought to understand the effects of intravitreally administered aflibercept on blood pressure and would have been motivated to consult other available aflibercept clinical data, including that reported in the FDA’s 2011 Clinical Pharmacology and Biopharmaceutics Review. For the same reasons I discuss in Section XIV regarding GROUND 5, the data in the 2011 Eylea® Clinical Review teaches a POSA that intravitreally administration of low dose aflibercept did not cause a significant increase in blood pressure.

389. A POSA would reasonably expect the lack of a significant increase in blood pressure after intravitreal administration of low dose Eylea® to also be the case for intravitreal injection of higher concentrations, 8 mg aflibercept (≥ 100 mg/ml) formulations taught by Furfine, Dix, the AU Eylea® Label, and Fiedler.

As I discuss in Sections XI.A and XII.A, a POSA would have reasonably expected intravitreal injection of higher-concentration aflibercept to have at least the same clinical effect as low dose Eylea®.

390. In my opinion, a POSA would have been motivated to combine Furfine, Dix, the AU Eylea® Label, Fiedler, Larson, and the 2011 Eylea® Clinical Review with a reasonable expectation of success making Claims 2 and 3 of the '036 patent obvious.

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

392. I currently hold the opinions expressed in this declaration. My analysis may continue, and I may acquire additional information and/or attain supplemental insights that may result in additional observations. I reserve the right

to offer additional opinions regarding the subject matter set forth in this declaration, including in response to any argument raised by Regeneron, or in response to expert opinions offered on behalf of Regeneron.

Dated: September 17, 2025

A handwritten signature in black ink, appearing to read "Donald J. D'Amico". The signature is fluid and cursive, with a prominent "D" and "A".

DONALD JOSEPH D'AMICO

EXHIBIT A

Curriculum Vitae Donald Joseph D'Amico

CURRICULUM VITAE

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Date of preparation: April 11, 2025

A. GENERAL INFORMATION

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Children's name and ages: Donald John D'Amico (42), Laura Kristine D'Amico (38), John Stephen D'Amico (34), Arianna Marie D'Amico (16)

Race/Ethnicity: Caucasian

B. EDUCATIONAL BACKGROUND

<i>Degree</i>	<i>Institution name, city and state</i>	<i>Dates attended</i>	<i>Year Awarded</i>
SB (Chemistry)	Massachusetts Institute of Technology, Cambridge, MA	9/68-6/72	1972
MD	University of Illinois College of Medicine, Chicago, IL (James Scholar program). 1973-74 in Neurochemistry research	9/72-6/77	1977

C. PROFESSIONAL POSITIONS AND EMPLOYMENT

Post-doctoral training including residency/fellowship

<i>Title</i>	<i>Institution name, city and state</i>	<i>Dates held</i>
Intern (Medicine)	Michael Reese Hospital, Chicago, IL	7/77-6/78
Resident (Ophthalmology)	Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA	7/78-8/81
Fellow (Vitreoretinal Diseases)	Bascom Palmer Eye Institute, University of Miami, Miami, FL	8/81-8/82

Academic positions (teaching and research)

<i>Title</i>	<i>Institution name, city and state</i>	<i>Dates held</i>
Clinical Fellow in Ophthalmology	Harvard Medical School, Boston, MA	7/78-8/81
Fellow in Ophthalmology	University of Miami, Miami, FL	8/81-8/82
Instructor in Ophthalmology	Harvard Medical School, Boston, MA	8/82-7/85
Assistant Professor of Ophthalmology	Harvard Medical School, Boston, MA	7/85-7/89
Associate Professor of Ophthalmology	Harvard Medical School, Boston, MA	7/89-7/99
Professor of Ophthalmology	Harvard Medical School, Boston, MA	7/99-11/06
Professor and Chairman Ophthalmology	Weill Cornell Medical College, Cornell University, New York, NY	Start 11/06

Hospital positions (e.g., attending physician, if applicable)

<i>Title</i>	<i>Institution name, city and state</i>	<i>Dates held</i>
Assistant Director of Residency Training	Massachusetts Eye and Ear Infirmary, Boston, MA	8/82-7/83
Assistant in Ophthalmology, Assistant Staff	Massachusetts Eye and Ear Infirmary, Boston, MA	8/82-7/85
Assistant in Ophthalmology, Associate Staff	Massachusetts Eye and Ear Infirmary, Boston, MA	7/85-7/86
Assistant Surgeon in Ophthalmology, Active Staff	Massachusetts Eye and Ear Infirmary, Boston, MA	7/86-7/87
Associate Surgeon in Ophthalmology, Active Staff	Massachusetts Eye and Ear Infirmary, Boston, MA	7/87-7/91
Assistant Chief of Ophthalmology for Clinical Affairs	Massachusetts Eye and Ear Infirmary, Boston, MA	7/90-11/06
Surgeon in Ophthalmology, Active Staff	Massachusetts Eye and Ear Infirmary, Boston, MA	1991-11/06
Clinical Associate in Surgery	Massachusetts General Hospital, Boston, MA	1996-11/06
Ophthalmologist-in-Chief	New York-Presbyterian Hospital, New York, NY	Start 11/1/06
Attending Physician in Surgery/Division of Ophthalmology	New York-Presbyterian Brooklyn Methodist Hospital, New York, NY	Start 5/25/21

Employment (other than positions listed above)

D. LICENSURE, BOARD CERTIFICATION, MALPRACTICE (if applicable)

Licensure

<i>State</i>	<i>Number</i>	<i>Date of Issue</i>	<i>Date of last registration</i>
NY	241673	8/29/06	Active

MA 47124
DEA number: BD1060906

1/12/81

Inactive 2007 nonrenewal

Board Certification

<i>Full Name of Board</i>	<i>Certificate #</i>	<i>Date</i>
American Board of Ophthalmology	NA	12/12/82

Malpractice insurance

Do you have Malpractice insurance? Yes

Name of Provider: MCIC Vermont

Premiums paid by: (self/ group/ institution (give name of group/institution))
Group: New York-Presbyterian/Weill Medical College

E. PROFESSIONAL MEMBERSHIPS (medical and scientific societies)

<i>Member/officer title</i>	<i>Name of Organization</i>	<i>Dates held</i>
Member	Association for Research in Vision and Ophthalmology	1980-present
Member	Massachusetts Eye and Ear Infirmary Alumni Association	1981-present
Member (Fellow)	American Academy of Ophthalmology	1982-present
Member	Society of Heed Fellows	1982-present
Member	American Diabetes Association	1982-present
Member	Bascom Palmer Eye Institute Alumni Association	1982-present
Member	Aspen Retinal Detachment Society	1982-present
Program Chair	Aspen Retinal Detachment Society	2000-present
Member	American Association for the Advancement of Science	1983-present
Member	New England Ophthalmological Society	1984-present
Member	American Medical Association	1984-present
Member	Massachusetts Medical Society	1984-present
Member	Massachusetts Society of Eye Physicians and Surgeons	1984-2007
Member	Retina Society	1986-present
Secretary	Retina Society	2000-2005

Vice-President	Retina Society	2005-2007
President	Retina Society	2007-2009
Member	International Society of Eye Research	1987-present
Member	PanAmerican Association of Ophthalmologists	1987-present
Member	Macula Society	1987-present
Member	American Uveitis Society	1987-present
Member	American Society of Retina Specialists (formerly the Vitreous Society)	1990-present
Member	Club Jules Gonin	1992-present
Executive Committee	Club Jules Gonin	2004-present
President	Club Jules Gonin	2009-2012
Member	Association of University Professors of Ophthalmology (AUPO)	2007-present
Member	New York Ophthalmological Society	2007-present
Member	The Ophthalmic Laser Surgical Society	2007-present
Fellow	The New York Academy of Medicine	2007-present
Member	The New York Clinical Society	2007-present
Member	New York State Ophthalmological Society	2007-present

F. HONORS AND AWARDS

<i>Name of award</i>	<i>Date awarded</i>
University of Illinois College of Medicine Research Award: "Direct Microdetermination of Manganese in Normal Serum and Cerebrospinal Fluid by Flameless Atomic Absorption Spectrophotometry"	1977
Heed Ophthalmic Foundation Scholarship	1981
Guest of Honor Lecture, "Intravitreal Drug Therapy: Clinical Considerations and Current Research," at the request of the Japanese Ophthalmological Society for their 92 nd Congress, Kyoto, Japan	1988
Honor Award, American Academy of Ophthalmology	1990
Invited Named Lecture, "Endophthalmitis: Clinical Management and Current Research" for the 1991 Illinois Society for the Prevention of Blindness Lectureship, presented at the 1991 Annual Meeting of the Chicago Ophthalmological Society	1991
Invited Named Lectureship, the Emory Retina Lecturer, "Endophthalmitis: New Perspectives on Prophylaxis and	1993

Management", "Retinal Manifestations of AIDS", and "Diagnosis and Management of Diabetic Traction Retinal Detachment" Emory University, Atlanta GA	
Teacher of the Year Award, given by the Residents of the Massachusetts Eye and Ear Infirmary	1995
Guest of Honor Lectures "Experience With An Erbium-YAG Laser For Vitreoretinal Surgery" and "Management of Proliferative Diabetic Retinopathy" at the request of the Korean Ophthalmological Society for their annual meeting, Seoul, Korea	1995
Invited Named Lecture, the Everett R. Veirs Lecture "Diagnosis and Management of Endophthalmitis" given at the Scott & White Clinic, Texas A & M University, Temple TX	1996
Invited Named Lecture, the Taylor R. Smith Lecture "Endophthalmitis 1997" given at 25th annual meeting of the Aspen Retinal Detachment Society, Snowmass, CO	1997
Teacher of the Year Award, given by the Residents of the Massachusetts Eye and Ear Infirmary	2000
Senior Achievement Award, American Academy of Ophthalmology	2002
Guest of Honor Lecture "Seeking New Possibilities in Vitreoretinal Surgery" for the 56 th Congress of Clinical Ophthalmology in Japan, Morioka, Japan	2002
Honor Award, the American Society of Retinal Specialists	2003
Invited Named Lecture, the Delbert P. Nachazel, Jr. Lecture "Vitreoretinal Surgery In Association With Permanent Keratoprosthesis" given at New Frontiers In The Management Of Retinal Diseases, Detroit, MI	2003
Invited Named Lecture, the Irving H. Leopold Lecture "Neovascular AMD: The Current Treatment Landscape" given at the 58 th Alumni Conference of the Wills Eye Hospital, Philadelphia PA	2006
Invited Named Lecture, the Nikolaos Stangos Lecture "Changing Concepts in the Treatment of Retinal Detachment" given at the 4 th Retina-Macula-Vitreous Hippocratic Symposium, Thessaloniki Greece	2006
Invited Named Lecture, the Robert Haimovici Lecture "Advances in the Diagnosis and Management of Age-related Macular Degeneration, given at Boston University Medical Center, Boston MA	2006
Invited Named Lecture, the McLean Lecture "New Clinical and Experimental Approaches in Retinal Vein Occlusions", Weill Cornell Medical College, New York NY	2007
Invited Named Lecture, the Robert Haimovici Lecture "Diabetic	2007

Retinopathy: Advances in Pathophysiology, Drug Treatment, and Vitreoretinal Surgery” Bascom Palmer Eye Institute, Miami FL	
Invited Keynote Lecture, “Diabetic Retinopathy: Advances in Pathophysiology, Medical and Laser Treatment, and Vitreoretinal Surgery” and “Evolutionary and Revolutionary Trends in Vitreoretinal Surgery” British and Eire Vitreoretinal Society, St. Andrews Scotland, UK	2007
Invited Named Lecture, the Victor T. Curtin Lecture “Retinal Detachment Surgery 2008: Current Perspectives from a Surgeon of the Bascom Palmer School”, Bascom Palmer Eye Institute, Miami FL	2008
Invited Named Lecture, the Taylor R. Smith Lecture “Retinal Detachment Surgery 2008: Current Perspectives From One Surgeon Who Used to Hold the Strings for Dr. Taylor R. Smith” presented to the New England Ophthalmological Society, Boston MA	2008
Fellow Award, Association of Research in Vision and Ophthalmology	2009
Invited Named Lecture, the 27 th Delta Gamma Lecture of the Houston Ophthalmological Society, “Advances in the Management of Retinal Detachment”, Houston TX	2009
Partnership Award, Lighthouse International	2009
Invited Named Lecture, the 12 th L. Edward Perraut Memorial Lecture, “Advances in the Management of Retinal Detachment”, the 2009 Washington Retina Symposium, Washington DC	2009
Invited Named Lecture, The Joseph Smiddy Lecture, “Progress in Vitreoretinal Surgery: Recent Advances and New Controversies”, Current Concepts in Ophthalmology, Wilmer Eye Institute, Baltimore MD	2009
Invited Named Lecture, the Gian Battista Bietti Medal Lecture, "Advances in the Management of Retinal Detachment" (given in Italian) at the 9th meeting of the Società Oftalmologica Italiana, Rome, Italy	2011
The 2012 Humes Visiting Professorship Award, presented by the Open Medical Institute of the American Austrian Foundation	2012
Invited Named Lecture, The Paul Sternberg, Jr. Lecture, "The Management of Retinal Detachment: Advances, Challenges, and Controversies" at the 27 th Southeastern Vitreoretinal Seminar (SEVR) meeting, Emory University, Atlanta GA	2013
Invited Named Lecture, The 2014 LuEsther T. Mertz Vitreous Retina Macula Lectureship “Confronting Our Limits in Vitreoretinal Surgery: Where We Are Stalled, and How We Might Improve” Manhattan Eye, Ear, and Throat Hospital, New York University,	2014

New York NY	
Life Achievement Honor Award presented by the American Academy of Ophthalmology at the Annual Meeting, Chicago IL	2014
Invited Visiting Professor, The Harvard Visiting Professorship in Ophthalmology, Lecture "Confronting Our Limits in Vitreoretinal Surgery: Where We Are Stalled, and How We Might Improve" Massachusetts Eye and Ear Infirmary, Boston MA	2015
Invited Named Lecture, "Advances and Controversies in the Management of Retinal Detachment" The I. Lee Arnold, MD Distinguished Visiting Professor, University of Tennessee Department of Ophthalmology, Memphis TN	2016
Invited Named Lecture and Research Award, The Gertrude D. Pyron Award of the Retina Research Foundation, "Permanent Keratoprosthesis and Complex Ocular Reconstruction: New Opportunities and Challenges for the Vitreoretinal Surgeon" presented at the annual meeting of the American Society of Retina Specialists, San Francisco CA	2016
Invited Named Lecture, "Global Health Initiatives in Ophthalmology: Observations by a Participant Late to the Game" The 5 th Annual J. Arch McNamara Lecture, Wills Eye Hospital, Philadelphia PA	2016
Invited Named Lecture, "Advances and Controversies in the Management of Retinal Detachment", The Morton F. Goldberg Lecture, University of Illinois, Chicago IL	2017
Distinguished Clinical Achievement Award of the Harvard Ophthalmology Alumni Association, and Lecture "Vitreoretinal Diseases: Observations from 36 years of Treating and Teaching" given at the 2017 Alumni Reunion, Massachusetts Eye and Ear Infirmary, Boston MA	2017
Invited Named Lecture, "Advances and Controversies in the Management of Retinal Detachment", The Winslow Family Retina Lecture, UT Southwestern "Crossroads in Ophthalmology" meeting, Dallas TX	2018
Lifetime Mentorship Award of the Vit-Buckle Society with lecture "Observations from 37 Years of Treating and Teaching Vitreoretinal Diseases and Surgery," at the VBS Annual Meeting, Las Vegas NV	2019
Invited Named Lecture, "Unanswered Questions in Macular Surgery", The William H. Knobloch Lecture, University of Minnesota (Virtual)	2020
Invited Named Lecture, "Advances and Controversies in the Management of Primary Retinal Detachment", The Edward E. Bruner Lecture, Case Western Reserve University, Cleveland OH	2021
Invited Keynote Lecture, "Unanswered Questions in Macular Surgery", at Milano Retina 2022, Milan Italy	2022
Invited Named Lecture, "Turning Points in the Management of Giant Retinal Tear:	2023

The Transformational Insights and Surgical Approaches of H. MacKenzie Freeman, MD”, The H. MacKenzie Freeman Lecture, and additional lecture “Cataract Surgery Complications: Comments on PreOperative, Intraoperative, and PostOperative Management from a Retina Colleague” given at the 791st meeting of the New England Ophthalmological Society, Boston, MA

Invited Named Lecture, “Giant Tears and Giant Retinotomies: The Remarkable Development of Radical Retinal Surgery”, The Gary S. Abrams Retina Lecture, Kresge Eye Institute, Detroit MI 2023

The J. Donald M. Gass Medal Award with lecture “Macular Surgery: The First Fifty Years” presented at the 57th annual meeting of the Retina Society, Lisbon, Portugal 2024

G. INSTITUTIONAL/HOSPITAL AFFILIATION

Primary Hospital Affiliation: New York-Presbyterian Hospital, Weill Cornell Medical College; Start 11/06

Other Hospital Affiliations: New York-Presbyterian Brooklyn Methodist Hospital; Attending the Department of Surgery/Division of Ophthalmology; Start May 2021

Other Institutional Affiliations:

H. EMPLOYMENT STATUS

Name of Current Employer(s): New York Presbyterian, Weill Cornell Medical College, Weill Cornell Eye Associates Start 11/1/06

Employment Status: Full Time salaried by Weill Cornell Start 11/1/06

I. CURRENT AND PAST INSTITUTIONAL RESPONSIBILITIES AND PERCENT EFFORT

<u>Departmental Teaching (specific teaching functions/courses taught)</u>	Dates
Harvard Medical School, and also (identical arrangement)	1982-2006
Weill Cornell Medical College	2006-present
As an attending physician in the Retina Service, I provide direct supervision for ophthalmology residents, retina fellows, and medical students rotating on my service as parts of the Ophthalmology Residency, Retina Fellowship, and Medical Student Elective programs. Each resident spends four months on my service, examining patients two half-days per week, assisting	

me at surgery one day per week, and performing laser treatments with me. Each retina fellow spends two years with me with a similar schedule but with additional responsibilities. Medical students spend one-three days per week for a variable period and observe all activities. I also supervise retina research fellows (ranging from one to three at any time) and assist with laboratory procedures, experimental design, data analysis, and manuscript preparation. To date, I have trained approximately 260 residents, 90 retinal fellows, and 18 research fellows.

Instructor in optics and refraction for incoming residents	1980
Chief Resident in Ophthalmology with weekly teaching rounds, Grand Rounds, microsurgical laboratory courses	1981-1982
Faculty, Ophthalmic Laser Course	1984
Faculty, Ocular Trauma Course	1985
Faculty, Ophthalmic Laser Course	1985
Faculty, Laser Therapy of Ocular Disease	1987
Faculty, Laser Therapy of Ocular Disease	1988
Faculty, Laser Therapy of Ocular Disease	1989
Faculty, Innovations in Cataract Surgery	1990
Faculty, Laser Therapy of Ocular Disease	1991
Chairman of the Continuing Medical Education Committee	1992-1993
Course Director, Advances in Genetic Eye Disease	1992
Course Director, Advances in Ophthalmic Diagnostic Technology	1993
Course Director, Controversies in Ophthalmology	1993
Faculty, Retina Workshop for Nurses and Technicians	1995
Invited Lecture, "Leading Edge Advances in the Medical and Surgical Treatment of Vitreoretinal Diseases" for the First Harvard Department of Ophthalmology Annual Meeting	2004

Clinical Care (duties)

	Dates
Attending Physician, Retina Service, and Director of the Diabetic Retinopathy Unit of the Massachusetts Eye and Ear Infirmary	1982-2006
Attending Physician, Retina Service, and Chair, Weill Cornell Medical College, New York-Presbyterian Hospital	2006-present

Administrative duties (including committees)

Hospital: Massachusetts Eye and Ear Infirmary

	Dates
Social Service Advisory Committee	1983-1985
Eye Pharmacy Committee (Chairman Sept 87 to Jan 91)	1984-1991
Library Committee	1984-2006
Member of IBM/MEEI Automated Medical Record Project	1987

Executive Committee, Hospital Information Systems	
MeSH: Board of Directors	1988-1989
Operating Room Committee (Chairman Jan 90 to Nov 2006)	1989-2006
Associate Chief of Ophthalmology for Clinical Affairs	1990-2006
Continuing Medical Education Committee (Chairman 92-93)	1992-1994
Board of Surgeons	1993-2006
Eye Service Executive Committee	1994-2006
Development: Member of 21st Century Campaign Executive Committee	1995-2006
Information Services Executive Committee	2001-2006
Information Services Board	2003-2006

Hospital: New York-Presbyterian Hospital

Executive Committee of the Medical Board	2006-present
Operating Room Committee	2006-present
Office of the Medical Board	2015-2019
Vice President WCMC Medical Board 2015-2017	2015-2017
President WCMC Medical Board and VP NYP Medical Board	2017-2018
President NYP Medical Board and ex-officio NYP Trustee	2018-2019
Member, DHK Steering Committee for Ambulatory Care	2017-present
Physician Advisor to the NYPH Board of Trustees Patient Safety and Quality Committee	2019-present

Medical School: Harvard Department of Ophthalmology

Executive Committee of the Harvard Dept. of Ophthalmology	1999-2006
Search Comm. for Director of Schepens Eye Research Institute	2002-2003
Chair, Search Comm: Professor, Diabetic Retinopathy Research	2003-2004
Search Committee for Professor of NeuroOphthalmology	2003-2005

Medical School: Weill Cornell Medical College

Executive Faculty Council	2006-present
Physician's Organization Operating Board	2006-present
Committee of Review	2007-2010
Member, Ambulatory Surgery Center Committee of PO	2007-2009
Member, Ophthalmology Chair Search, The Methodist Hospital, Houston TX	2008-2009
Member, Griffis Faculty Club Board of Directors	2008-2011
Member, PO Growth Task Force	2010-2011
Member, Medicine Chair Search Committee	2012-2013
Member, Committee to revise WCMC promotion criteria	2014-2015
Chair, Committee for Standards 1 and 2, LCME review	2016-2018

Member, David H, Koch Ambulatory Center Steering Committee 2016-present

Research

	Dates
Howe Laboratory of Ophthalmology/Laser Research Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA	1982-2006
Margaret M. Dyson Vision Research Institute, Director	2006-2010 2015-present

Current percent effort	%	Does the activity involve WCMC students/researchers? (Yes/No)
Teaching	15	Yes
Clinical Care	50	Yes
Administration	20	NA
Research	15	Yes
Total	100%	NA

J. RESEARCH SUPPORT (past and present)

Source	Amount	Date	Name of Principal Investigator
National Institutes of Health/NEI	\$107,500.00	8/1/82-7/31/85	Donald J. D'Amico

Individual's role in project including percent effort
Principal Investigator, 70% effort
Title: NIH R23 EY04474 "Retinal Toxicity of Intravitreal Gentamicin"

Source	Amount	Date	Name of Principal Investigator
National Institutes of Health/NEI	\$339,604.00	8/1/85-7/31/88	Donald J. D'Amico

Individual's role in project including percent effort
Principal Investigator, 50% effort
Title: NIH R01 EY04474 "Retinal Toxicity of Intravitreal Antibiotics"

Source	Amount	Date	Name of Principal Investigator
Milton Fund Harvard	\$1,500.00	1983-1984	Donald J. D'Amico

Individual's role in project including percent effort
Co-Principal Investigator, 5% effort
Title: "Experimental Model of Diabetic Retinopathy"

Source	Amount	Date	Name of Principal Investigator
American Diabetes Association	\$5,000.00 (est)	1985-1987	Donald J. D'Amico

Individual's role in project including percent effort

Co-Principal Investigator, 5% effort

Title: "Applications of Nuclear Magnetic Resonance to Diabetic Retinopathy Research"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Lions Eye Research Fund	\$5,000.00 (est.)	1990-1991	Nancy H. Kolodny

Individual's role in project including percent effort

Co-Investigator, 5%

Title: "Development of Applications of MRI and MRS to the Diagnosis of Eye Diseases"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
National Institutes of Health/NEI	\$35,000.00 (est.)	1991-1995	Donald J. D'Amico

Individual's role in project including percent effort

Principal Investigator, 5%

Title: NEI EY08587-03 Endophthalmitis Vitrectomy Study, Clinical Center

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Lions Eye Research Fund	\$5,000.00 (est.)	1991-1992	Nancy H. Kolodny

Individual's role in project including percent effort

Co-Investigator, 5%

Title: "Research Program in Magnetic Resonance"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Lions Eye Research Fund	\$5,000.00 (est.)	1993-1994	Donald J. D'Amico

Individual's role in project including percent effort

Principal Investigator, 5%

Title: "Retinal Adhesives for Vitreoretinal Surgery"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
The Foundation of Mass Eye and Ear Infirmary and Coherent Medical, Inc.	\$180,000.00 (est.)	1993-2006	Donald J. D'Amico

Individual's role in project including percent effort

Principal Investigator, 10%

Title: "Erbium-YAG Laser for Vitreoretinal Surgery"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
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Lions Eye Research Fund	\$5,000.00 (est.)	1994-1995	Donald J. D'Amico
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Individual's role in project including percent effort

Co-Principal Investigator, 5%

Title: "Preclinical Investigations in Vitreoretinal Disease"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Lions Eye Research Fund	\$5,000.00 (est.)	1995-1996	Donald J. D'Amico

Individual's role in project including percent effort

Co-Principal Investigator, 5%

Title: "Digital Image Processing: Combined Technology for Neovascularization Research"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Lions Eye Research Fund	\$5,000.00 (est.)	1996-1997	Donald J. D'Amico

Individual's role in project including percent effort

Principal Investigator, 5%

Title: "The Control of Severe Inflammation in Pneumococcal Endophthalmitis"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Lions Eye Research Fund	\$5,000.00 (est.)	1997-1998	Donald J. D'Amico

Individual's role in project including percent effort

Principal Investigator, 5%

Title: "The Search for Anti-inflammatory Medication in the Treatment of Candidal Endophthalmitis"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
The Iacocca Foundation	\$500,000.00 (est.)	2000-2003	Donald J. D'Amico

Individual's role in project including percent effort

Co-Principal Investigator, 10%

Title: "Experimental Studies on Diabetic Retinopathy"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Lions Eye Research Fund	\$5,000.00 (est.)	2001-2002	Donald J. D'Amico

Individual's role in project including percent effort

Principal Investigator, 5%

Title: "Microsurgery to Reopen Blocked Branch Veins in the Retina"

<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Research to Prevent Blindness	\$220,000	2007-2011	Donald J. D'Amico
<i>Individual's role in project including percent effort</i>			
Principal Investigator, 5%			
Title: Departmental Challenge Grant			
<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Regeneron Pharmaceuticals, Inc.	\$36,528.45	2007-2009	Donald J. D'Amico
<i>Individual's role in project including percent effort</i>			
Principal Investigator, 2%			
Title: Clinical Center for Intravitreal VEGF-Trap for Neovascular AMD			
<i>Source</i>	<i>Amount</i>	<i>Date</i>	<i>Name of Principal Investigator</i>
Research to Prevent Blindness	\$115,000/yr	2011-present	Donald J. D'Amico
<i>Individual's role in project including percent effort</i>			
Principal Investigator, 5%			
Title: Unrestricted Departmental Grant			

K. EXTRAMURAL PROFESSIONAL RESPONSIBILITIES

Committee Assignments in Professional Societies

ARVO Program Planning Committee: Retina Section (Chair 1991)	1988-1991
American Board of Ophthalmology: Associate Examiner	1992
Retina Society: Credentials Committee (Chair 1996-2000)	1992-2000
Club Jules Gonin: Abstract Review/Program Committee	2002-present
Research to Prevent Blindness Ad hoc Grant Review Committee	2007, 2010

Committee Assignments in Clinical Research

Member of the Independent Data Safety Monitoring Committee for 1) Prophylactic Laser Treatment for Age-related Macular Degeneration Trial (1998-), and 2) Transpupillary Thermotherapy Trial for Age-related Macular Degeneration (2000-), both sponsored by Iridex.	1998-2005
Chairman, IDMC for Anecortave Acetate for Age-related Macular Degeneration Trials, sponsored by Alcon Labs.	2000-2008
Member, IDMC for Macugen for Age-related Macular Degeneration Trials, sponsored by Eyetech Pharmaceuticals, Inc.	2001-2007

Presenter before FDA Advisory committee for pegaptanib (Macugen) for age-related macular degeneration new drug application (Risk/Benefit section) August 27, 2004	2004
Chairman, IDMC for CNTF trials in Age-related Macular Degeneration and Retinitis Pigmentosa, sponsored by Neurotech, Inc.	2006-2011
Presenter before FDA Advisory committee for ranibizumab (Lucentis) for diabetic macular edema new drug application (An Unmet Clinical Need) July 26, 2012	2012

Editorial Boards

<i>Seminars in Ophthalmology</i>	1990-present
<i>Retina</i>	1991-2016
<i>Ophthalmic Surgery, Lasers, and Imaging</i>	1995-present
<i>Digital Journal of Ophthalmology</i>	1996-2002
<i>Journal of VitreoRetinal Diseases</i> Inaugural Editor-in-Chief	2016-present

Professional Leadership Roles Related to Teaching

Since 1987, I have sponsored and served as co-director for a yearly seminar Nantucket Retina. This two-day meeting is attended by approximately 50 retina specialists from around the world. My responsibilities include evaluation of abstracts, assembling the program, and moderating one day of this seminar.	1987-present
In 1990, I served as Program Director, Moderator, and Faculty for the Retina Subsection of the Northeastern Regional Update Course of the American Academy of Ophthalmology. My role for this two-day meeting included selection of themes for presentation, invitation of speakers, coordination and review of all written syllabi, and program moderation.	1990
Since 2000, I have served as the Program Chairman for the Aspen Retinal Detachment Society meeting. My responsibilities include selection of all speakers and thematic development of the program for this week-long conference.	2000-present
In 2001, I served as Program Chair for the Retina Society Annual Meeting in Chicago, which was to have been held Sept 13-16, but was cancelled due to 9/11. My role included responsibility for assembling all scientific, technological, and social details for this program.	2001

- In 2002, I served as Co-Program Chair for the Retina Congress 2002 in San Francisco, the combined meeting of the Retina and Vitreous Societies. This meeting was the largest independent retinal meeting held to date, and my role included central responsibility for the scientific, technological, and social details for this program. 2002
- In 2003, I served as Program Chair for the Retina Society Annual Meeting in Chicago, which included more than 500 participants. My role included responsibility for assembling all scientific, technological, and social details for this program. 2003
- In 2004, I served as Program Chair for the Retina Society Annual Meeting in Baltimore, which included more than 500 participants. My role included responsibility for assembling all scientific details as well as corporate participation for this program. 2004
- In 2005, I served as Program Chair for the Retina Society Annual Meeting held in San Diego, which included more than 500 participants. My role included responsibility for assembling all scientific details as well as corporate participation for this program. 2005
- In 2006, I served as Program Chair for the Retina Society/Club Jules Gonin Combined Annual Meeting held in Cape Town, South Africa, which included more than 500 participants. My role included responsibility for assembling all scientific details for this program. 2006
- In 2007, I served as Program co-Chair for the 40th Anniversary Retina Society Annual Meeting held in Boston, which included more than 400 participants. My role included shared responsibility for assembling all scientific details for this program. 2007
- In 2008, I served as Program co-Chair for the 41st Anniversary Retina Society Annual Meeting held in Scottsdale, which included more than 300 participants. My role included shared responsibility for assembling all scientific details for this program.

In 2009, I served as Meeting Initiator and Program Co-Chair for the Retina Congress 2009, a combined meeting of the Retina Society, the Macula Society, and the American Society of Retina Specialists held in New York. This meeting was the largest-ever independent meeting of retina specialists and included more than 1700 participants. My role included shared responsibility for assembling all scientific details for this program.

L. BIBLIOGRAPHY

Peer Reviewed Articles

1. Klawans HL, **D'Amico DJ**, Patel BC: Behavioral supersensitivity to 5-hydroxytryptophan induced by chronic methysergide pretreatment. *Psychopharmacologia* 44:297-300, 1975.
2. **D'Amico DJ**, Calne DB, Klawans HL: Altered hypothermic responsiveness to (+)-amphetamine. *Journal of Pharmacy and Pharmacology* 28:154-156, 1976.
3. **D'Amico DJ**, Patel BC, Klawans HL: The effect of methysergide on 5-hydroxytryptamine turnover in whole brain. *Journal of Pharmacy and Pharmacology* 28:454-456, 1976.
4. **D'Amico DJ**, Klawans HL: Direct microdetermination of manganese in normal serum and cerebrospinal fluid by flameless atomic absorption spectrophotometry. *Analytical Chemistry* 48:1469-1472, 1976.
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65. Rutar T, Reinke MH, D'Amico DJ, Bhisitkul RB. Diseases of the Vitreous. In Principles and Practice of Ophthalmology, Third Edition, Albert DM and Jakobiec FA, eds., Saunders Elsevier, Philadelphia, PA, vol. 2, pp 22387-2401, 2008.
66. McMullen WW, D'Amico DJ. AIDS and Its Ophthalmic Manifestations. (revision) In Principles and Practice of Ophthalmology, Third Edition, Albert DM and Jakobiec FA, eds., Saunders Elsevier, Philadelphia, PA, vol. 4, pp 4699-4716, 2008.
67. Port AD, Orlin A, Kiss S, Patel S, D'Amico DJ, Gupta MP. Cytomegalovirus Retinitis: A Review. J Ocul Pharmacol Ther. 2017;33:224-234.
68. Kovacs KD, D'Amico DJ. Giant Retinal Tears. (revision) In Principles and Practice of Ophthalmology, Third Edition, Albert DM and Jakobiec FA, eds., Saunders Elsevier, Philadelphia, PA, https://doi.org/10.1007/978-3-319-90495-5_99-1, 2021.
69. D'Amico DJ. A Brief History of Macular Surgery. Patelli F and Rizzo S 2024 in press.

Major Reviews

1. **D'Amico DJ.** Diseases of the Retina. *New England Journal of Medicine* 1994;331:95-106.
2. **D'Amico DJ.** A 58 year old woman with unilateral loss of vision and postmenopausal bleeding. Case Records of the Massachusetts General Hospital, *New England Journal of Medicine* 2002;346:189-195.
3. **D'Amico DJ.** Primary Retinal Detachment. *New England Journal of Medicine* 2008;359:2346-2354.
4. Klufas MA, Yannuzzi NA, **D'Amico DJ**, Kiss S. Vitreoretinal aspects of permanent keratoprosthesis. *Surv Ophthalmol* 2015;60:216-228.

5. Port AD, Orlin A, Kiss S, Patel S, **D'Amico DJ**, Gupta MP. Cytomegalovirus retinitis: a review. *J Ocul Pharmacol Ther* 2017;33:224-234.
6. **D'Amico DJ**. Permanent keratoprosthesis and complex ocular reconstruction: new opportunities and challenges for the vitreoretinal surgeon. The Gertrude D. Pyron 2016 Award Lecture of the American Society of Retina Specialists. *J VitreoRetinal Dis* 2017;1; 159-168.

Proceedings of Meetings, Correspondence

1. **D'Amico DJ**, Libert J, Kenyon KR, Caspers-Velu L, Shanks E, Hanninen LA: Retinal toxicity of intravitreal aminoglycoside antibiotics: differential susceptibility of the retinal pigment epithelium to drug toxicity. Proceedings of the VIIth Congress of the European Society of Ophthalmology, Helsinki, Finland, pp 96-98, 1984.
2. Libert J, **D'Amico DJ**, Kenyon KR: Diagnosis of lysosomal storage diseases by the ultrastructural study of conjunctival biopsies. *ibid*, pp 239-241.
3. Kenyon KR, Libert J, **D'Amico DJ**: Drug-induced lysosomal disorders affecting the eye. *ibid*, pp 242-245.
4. **D'Amico DJ**, Libert J, Kenyon KR: Inherited and drug-induced lysosomal disorders affecting the eye. Proceedings of the Japanese Ophthalmological Society, Excerpta Medica International Congress Series (K. Mizuno, ed.) 671:53-60, 1984.
5. Smith EV, Kolodny NH, Gragoudas ES, Rubin LG, Seddon JM, **D'Amico DJ**: Safety and effectiveness of magnetic resonance imaging of choroidal melanoma patients with episcleral tantalum rings after proton beam irradiation. *American Journal of Ophthalmology* (Letter) 105:695-696, 1988.
6. **D'Amico DJ**, Kolodny NH, Gragoudas ES, Kohler SJ, Seddon JM, Albert DM, Murphy EJ, Yun C: Multinuclear magnetic resonance imaging of human ocular melanoma. In Tumors of the Eye; Proceedings of the 2nd International Meeting on Diagnosis and Treatment of Intraocular Tumors, Kugler publications, editors Bornfeld N, Gragoudas ES, Höpping W, Lommatzsch PK, Wessing A, and Zografos L, pp 323-328, 1989.
7. Ciulla TA, **D'Amico DJ**, Miller JW: Laser photodisruption of visible retinal artery

emboli. *British Journal of Ophthalmology* (Letter) 79:964, 1995.

8. Kwak HW, **D'Amico DJ**: Determination of dexamethasone sodium phosphate in the vitreous by high performance liquid chromatography. *Korean Journal of Ophthalmology* 9:79-83, 1995.
9. Friedman ES, D'Amico DJ. Letter from H Buettner and response regarding Friedman and D'Amico article #58 above "Vitreotomy alone for the management of uncomplicated recurrent retinal detachments." *Retina* 1996;16:347-348.
10. Ng EW, **D'Amico DJ**: Therapeutic efficacy of intravitreal ceftazidime, imipenem, and amikacin in a swine model of posttraumatic *Pseudomonas aeruginosa* endophthalmitis. *Retina* (Letter) 17:464-5, 1997.
11. **D'Amico DJ**, Friberg TR. Limited inferior macular translocation for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Am J Ophthalmol* (Letter) 2001;132:289.

Invited Discussions

1. Contributing discussant, Case Records of the Massachusetts General Hospital, "Histiocytic Lymphoma of the Eye," *New England Journal of Medicine* 313:436-443, 1985.
2. Discussant, American Academy of Ophthalmology 1986 Annual Meeting, "Treatment of Cytomegalovirus Retinitis with Ganciclovir," *Ophthalmology* 94:822-823, 1987.
3. Discussant, American Academy of Ophthalmology 1988 Annual Meeting, "Results of Vitrectomy for Diabetic Traction Retinal Detachment Using the En Bloc Excision Technique."
4. Discussant, American Academy of Ophthalmology 1989 Annual Meeting, "Surgical Management of Complications of Proliferative Sickle Retinopathy without Exchange Blood Transfusion."
5. Discussant, American Academy of Ophthalmology 1993 Annual Meeting, "Ocular Involvement in Candidemic Patients."

Book Reviews

1. "Retinal Detachment Surgery" by James Schutz, Raven Press, 1984, published in

Archives of Ophthalmology 103:1637, 1985.

2. "Posterior Uveitis and Retinitis" videotape by G. Richard O'Connor, Mark S. Blumenkranz, and W. W. Culbertson, American Academy of Ophthalmology, San Francisco, 1984, published in *Archives of Ophthalmology* 104:649, 1986.
3. "Goldberg's Genetic and Metabolic Diseases" edited by William A. Renie and Morton F. Goldberg; Little Brown and Company, 1986, published in *Archives of Ophthalmology* 105:180, 1987.

Abstracts, Presentations:

Invited Regional, National, or International Contributions

1980

Paper Presentation, "Amiodarone Keratopathy: A Drug-induced Lipid Storage Disorder" Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota FL

1981

Paper Presentation, "Lipid Inclusions in Human Conjunctiva in Tissue Culture Induced by Standard Antibiotics", Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota FL

Invited Speaker, "Lipid Inclusions in Human Ocular Tissues in Vitro Induced by Aminoglycoside Antibiotics" International Symposium on Genetics in Ophthalmology, Jerusalem, Israel

1983

Paper Presentation, "Retinal Toxicity of Gentamicin after Intravitreal Injection: Evidence of Lysosomal Impairment in RPE and Retina", Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota FL

Paper Presentation, "Retinal Toxicity of Aminoglycoside Antibiotics" at the 17th Annual Meeting of the Retina Society, Detroit MI

Paper Presentation, "Diabetic Retinopathy Panretinal Photocoagulation and the Electroretinogram" American Academy of Ophthalmology, Chicago IL

1985

Visiting Professor, Beaumont Hospital, Detroit MI

Paper Presentation, "Treatment of CMV Retinitis with BW-B759U (DHPG)" at the 18th Annual Meeting of the Retina Society, Cleveland OH

1986

Paper Presentation, "Evaluation of Potential Increase in Traction with Panretinal Photocoagulation", 5th Vail Vitreoretinal Seminar, Vail CO

Paper Presentation, "Retinal Toxicity of Intravitreal Aminoglycoside Antibiotics: Pathophysiology, Drug Comparison, and Influence of Vitreous Surgery" 7th International Congress of the International Society for Eye Research, Nagoya, Japan

Visiting Professor, Kanazawa University, Kanazawa, Japan

Visiting Professor, Emory University, Atlanta GA

Faculty, American Academy of Ophthalmology Course 605 "Infectious Diseases of the Retina and Choroid"

1987

Course Director, Nantucket Retina

Paper Presentation, "Multinuclear Magnetic Resonance Imaging of Human Ocular Melanoma" at the 20th Annual Meeting of the Retina Society, Southampton Bermuda

Faculty, American Academy of Ophthalmology Course 108 "Medical and Surgical Management of Endophthalmitis"

1988

Faculty, Midwinter Laser Course and Fluorescein Angiography Workshop, Washington University, St. Louis, MO.

Faculty, Aspen Retinal Detachment Society

Course Director, Nantucket Retina

Paper Presentation, "Macula-threatening Diabetic Traction Retinal Detachment and Argon Panretinal Laser Photocoagulation" at the 21st Annual Meeting of the Retina Society, Philadelphia PA

Paper presentation, "Bacterial Endophthalmitis: New Observations Regarding Vitrectomy and Intravitreal Antibiotic Therapy, XVIth Meeting of the Club Jules Gonin, Bruges, Belgium

Faculty, American Academy of Ophthalmology Course 548 "Medical and Surgical Management of Endophthalmitis"

1989

Visiting Professor, Brooke Army Medical Center, Wilford Hall, and the University of Texas at San Antonio, TX

Faculty, Massachusetts Eye and Ear Infirmary Course "Selected Topics in Ophthalmology" Puerto Vallarta, Mexico

Paper Presentation, "Bacterial Endophthalmitis: Vitreous Surgery and Antibiotic Therapy", 6th Vail Vitreoretinal Seminar, Vail CO

Faculty, Academy Special Focus Course, Posterior Segment Laser Therapy, Duke University Eye Center, Durham, North Carolina

Paper Presentation, "Endophthalmitis: New Considerations in Diagnosis and Therapy" at the First Aegean Retina Meeting, Crete, Greece

Course Director, Nantucket Retina

Paper Presentation, "Bacterial Endophthalmitis: New Considerations in Intravitreal and Systemic Therapy" at the combined 22nd Annual Meeting of the Retina Society and the Annual Meeting of the Macula Society, Boston MA

Faculty, American Academy of Ophthalmology Course 218 "Medical and Surgical Management of Endophthalmitis"

Invited Faculty, Current Concepts in Ophthalmology for the Primary Care Physician, Saudi-Aramco Medical Services Organization, Dhahran, Saudi Arabia

1990

Faculty, Aspen Retinal Detachment Society

Invited Lecturer, "Viral Infections of the Retina," "Endophthalmitis: Clinical Spectrum and Diagnostic Approaches," "Endophthalmitis: Practical Medical and Surgical Treatment" Albany Medical College, Albany NY

Invited Lecturer, Dallas Spring Ophthalmology Symposium

Visiting Professor, Monterrey, Mexico

Invited Lecturer, Rhode Island Chapter of American Diabetes Association, Newport, Rhode Island

Invited Lecturer, New England Ophthalmological Society, Symposium on Ocular Trauma

Course Director, Nantucket Retina

Paper presentation, "Vitreotomy for Endophthalmitis: Influence of Surgery on Intravitreal Antibiotic Therapy" XVIIth Meeting of the Club Jules Gonin, Lausanne, Switzerland

Visiting Professor, Eye and Ear Institute, University of Pittsburgh, Pittsburgh PA

Program Director, Moderator, and Faculty for the Retina Subsection of the Northeastern Regional Update Course, American Academy of Ophthalmology, June 22-23

Faculty, Lancaster Course in Ophthalmology

Faculty, Course HO-212 "Laser Lab: Use of Binocular Indirect Ophthalmoscope Laser Delivery Systems" and Course 654 "Medical and Surgical Management of Endophthalmitis" at the Annual Meeting of the American Academy of Ophthalmology, Atlanta GA

Visiting Professor, Wills Eye Hospital, Philadelphia PA

Faculty, New England Ophthalmological Society Course for Ophthalmic Technicians, Boston MA

1991

Faculty, Massachusetts Eye and Ear Infirmary "Innovations in Clinical Ophthalmology" Maui, Hawaii

Faculty, New England Ophthalmological Society, "Problems in Retinal Photocoagulation" Boston, MA

Faculty, New England Ophthalmological Society, "Vitreous Surgery for Proliferative Diabetic Retinopathy" Boston, MA

Course Director, Nantucket Retina

Faculty, Medical and Surgical Retina in the 1990s, sponsored by Jules Stein Eye Institute and Doheny Eye Institute, Los Angeles, CA

Faculty, Symposium on Viral Retinitis and Retinal Disease in Immunosuppressed Patients, "Differential Diagnosis of Infectious Retinitis;" Faculty, Course HO-309, 346, 365 "Retinal Laser Application Laboratory: Use of Binocular Indirect Ophthalmoscope Laser Delivery System;" and Faculty, Course 462 "Medical and Surgical Management of Endophthalmitis" at the Annual Meeting of the American Academy of Ophthalmology, Los Angeles, CA

Visiting Professor, Kellogg Eye Center, the University of Michigan, Ann Arbor, MI

Invited Lecturer, Manhattan Eye, Ear, and Throat Hospital, New York, NY

1992

Invited Lecturer, Michigan Ophthalmological Society, Detroit, MI

Paper presentation, "Strategies for Photo-Occlusion of Retinal Neovascularization and Retinal Vascular Lesions by Direct Laser Photocoagulation" at the 15th Annual Macula Society meeting, Scottsdale AZ.

Invited Lecturer, "Early Vitrectomy in Proliferative Diabetic Retinopathy" at the 25th Panhellenic Ophthalmological Congress, Halkidiki, Greece

Faculty, Practical Ophthalmology for Primary Care, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

Course Director, Nantucket Retina

Paper presentation, "Candida Endophthalmitis: Experimental Evaluation of Vitreous Biopsy Techniques and Comparison of Therapy with Amphotericin B

versus Fluconazole” for the XVIIIth meeting of the Club Jules Gonin, Vienna, Austria

Faculty, Laser Therapy of Ocular Disease, New England Eye Center, Tufts University School of Medicine, Boston, MA

Faculty, “Changing Trends in Endophthalmitis Prophylaxis in Cataract Surgery”, The Vitreoretinal Frontier, Dallas, TX

Faculty, Course 515 "Medical and Surgical Management of Endophthalmitis"; Course 657 "Everything Was Going Just Fine Until"; and HO-427, 470, and 471 "Retinal Laser Application Laboratory: Use of Binocular Indirect Laser Delivery System" at the Annual Meeting of the American Academy of Ophthalmology, Dallas, TX

1993

Faculty, Squaw Valley Retina Symposium, Squaw Valley, CA

Invited Lecturer, the New York Hospital-Cornell Medical Center, New York, NY

Visiting Professor, University of Virginia, Charlottesville, VA

Invited Lecturer, Ophthalmic Club of Philadelphia, Philadelphia PA

Invited Lecturer, “Acute Retinal Necrosis” for the 26th Panhellenic Ophthalmological Congress, Crete, Greece

Invited Lecturer, Medical College of Wisconsin, Annual Meeting of the Eye Institute, Milwaukee, WI

Course Director, Nantucket Retina

Paper Presentation, “The Use of Lasers for Membrane Transection and Ablation in Vitreoretinal Surgery” at the IIIrd Aegean Retina Meeting, Samos, Greece

Paper Presentation, “Experimental Vitreoretinal Surgery with the Erbium-YAG Laser” at the 26th Annual Meeting of the Retina Society, San Francisco CA

Faculty, “Observations on the Management of Diabetic Traction Detachment”, New Dimensions in Retina, Chicago, IL

Faculty, Course 414, "Everything Was Going Just Fine Until..." American Academy of Ophthalmology Annual Meeting, Chicago, IL

1994

Faculty, Midwinter Laser Course and Fluorescein Angiography, St. Louis, MO

Invited Speaker, Utah Ophthalmological Society Annual Meeting, Park City, Utah

Faculty, Aspen Retinal Detachment Society

Invited Speaker, "Macular Damage with Intravitreal Drug Therapy" 3rd Meeting of the European Macular Group, Athens Greece

Invited Speaker, "Diagnosis and Treatment of Endophthalmitis" Societas Ophthalmologica Mediterranea 3rd International Congress, Athens Greece

Faculty, Update on Retinal Diseases for the Anterior Segment Surgeon, Newport, RI

Course Director, Nantucket Retina

Paper presentation, "Experimental Vitreous Surgery with the Erbium-YAG Laser" for the XIXth meeting of the Club Jules Gonin, Versailles, France

Paper Presentation, "Vitreoretinal Surgery with the Erbium-YAG Laser: Observations in Experimental Animal Surgery and in Patients" at the 27th Annual Meeting of the Retina Society, Colonial Williamsburg VA

Faculty, "Erbium-YAG Laser for Vitreoretinal Surgery", The Vitreoretinal Interface, San Francisco, CA

Faculty, Posterior Segment Complications of Anterior Segment Surgery; Faculty, Course 217, "Everything Was Going Just Fine Until...", American Academy of Ophthalmology Annual Meeting, San Francisco, CA

1995

Faculty, Vitreoretinal Update Course, Sarasota Retina Institute, Sarasota, FL

Invited Lecturer, New England Eye Center, Tufts University School of Medicine, Boston, MA

Invited Lecturer, "Erbium-YAG Laser Surgery of the Vitreous and Retina", Xth Congress of the European Society of Ophthalmology, Milan, Italy

Paper Presentation, "Clinical Experience with an Erbium-YAG Laser for Vitreoretinal Surgery" at the IVth Aegean Retina Meeting, Santorini, Greece

Course Director, Nantucket Retina

Paper Presentation, "Vitreoretinal Surgery with the Erbium-YAG Laser" at the 28th Annual Meeting of the Retina Society, Santa Fe NM

Faculty, Co-Moderator of Panel on Primary Retinal Detachment, The Cutting Edge, Atlanta, GA

Invited Lecture "Antibiotics and Retinal Disease" and Faculty, Course 622 "Everything Was Going Just Fine Until...", American Academy of Ophthalmology Annual Meeting, Atlanta, GA

1996

Course Coordinator "Ocular and Adnexal Infections" at the Massachusetts Eye and Ear Infirmary, Boston, MA

Invited Lecturer, Georgia Society of Ophthalmology Annual Meeting, Sea Island, GA

Invited Lecturer, the Sally Letson Symposium "Medical and Surgical Retina," Ottawa, Ontario, Canada

Invited Lecturer, Houston Ophthalmological Society, Houston, TX

Course Director, Nantucket Retina

Paper Presentation, "Intraocular Surgery with a High-repetition Rate Erbium-YAG Laser", for the joint XXth meeting of the Club Jules Gonin and the 29th annual meeting of the Retina Society, Bern, Switzerland

Faculty, Moderator for Panel Discussion on Primary Retinal Detachment, Vitreoretinal Frontiers: 21st Century, Chicago, IL

Faculty, Course 419 "Everything Was Going Just Fine Until...", American Academy of Ophthalmology Annual Meeting, Chicago, IL

Invited Lecturer, "Current Management of Diabetic Retinopathy", Instituto De Microcirugia Ocular De Barcelona, Barcelona, Spain

Invited Lecturer, "Ocular Surgery with the Erbium-YAG Laser: Vitreoretinal Experience in Patients and Future Frontiers", at the request of the Catalan Ophthalmological Association for the 27th Annual Congress, Barcelona, Spain

1997

Invited Lecture, "Erbium-YAG Laser for Vitreoretinal Surgery" at the request of the Ophthalmic Laser Surgical Society, New York, NY

Invited Lecture, "Failing or Failed Vitreoretinal Surgery for Severe Proliferative Vitreoretinopathy or Proliferative Diabetic Retinopathy," New England Ophthalmological Society, Boston, MA

Faculty, "Rétine médicale et chirurgicale: développments recents," Hôpital Cantonal Universitaire de Genève, Geneva, Switzerland

Invited Lecture, "New Ocular Surgical Approaches With The Erbium-YAG Laser" at the request of the Hellenic Ophthalmological Society for the 30th Panhellenic Congress, Vouliagmenis, Greece

Invited Lecture "Frontiers In Vitreoretinal Surgery" at the request of the Canadian Retina Vitreous Society, Quebec City, Canada

Course Director, Nantucket Retina

Invited Lectures "Retained Lens Fragments after Phacoemulsification: Management" and "Uveitis after Anterior Segment Surgery: Differential Diagnosis with Endophthalmitis and Treatment" for the Fifth International Congress of the Fondazione G. B. Bietti, Rome, Italy

Faculty, Moderator of Panel Discussion on Management of Posterior Segment Complications of Anterior Segment Surgery, Vitreoretinal Update 1997, sponsored by the American Academy of Ophthalmology, San Francisco, CA

Faculty, Course 462 "Everything Was Going Just Fine Until...", American Academy of Ophthalmology Annual Meeting, San Francisco, CA

1998

Invited Lecturer, Greater New York Ophthalmology Clinical Lecture Series,
"Endophthalmitis and Uveitis," New York, NY

Faculty, Diabetic Retinopathy Update, Cleveland Clinic Eye Center, Cleveland,
OH

Faculty, Second International Symposium on Macular Edema, Lausanne,
Switzerland

Invited Lecture "Medical and Surgical Management of Cystoid Macular Edema
after Cataract Extraction" at the request of the Ophthalmological Society of
Northern Greece for the 31st Panhellenic Ophthalmological Congress, Porto
Karras, Greece

Faculty, "Options for Intraoperative Retinal Photocoagulation", "Retinal
Photocoagulation in Diabetic Retinopathy", "Erbium-YAG Tissue Interactions",
"Ocular Surgery with the Erbium-YAG Laser", Second Annual Advanced
Ophthalmic Laser Surgery Course, Luzern, Switzerland

Course Director, Nantucket Retina

Paper presentation, "Perfluorocarbon Liquid Utilization for Primary Vitrectomy
Repair of Pseudophakic Retinal Detachment with Undetected Retinal Breaks"
as sponsoring co-author to P Brazitikos for the XXIst meeting of the Club Jules
Gonin, Edinburgh, Scotland

Faculty, Moderator of Panel Discussion on Primary Retinal Detachment,
Vitreoretinal Update, American Academy of Ophthalmology Annual Meeting,
New Orleans LA

1999

Faculty, Vitreoretinal Update Course, Sarasota Retina Institute, Sarasota, FL

Faculty, Aspen Retinal Detachment Society

Faculty, Practical Aspects and New Horizons in Retina and Vitreous, Asociación
para Evitar la Ceguera en México, Mexico City, Mexico

Keynote Speaker, "Endophthalmitis: Clinical Challenges and Current Research",
"Current Treatment of Dropped Nuclei and Dislocated IOLs", "Ocular Surgery
with the Erbium-YAG Laser" Comprehensive Eye Care, New Zealand--Royal

Australian College of Ophthalmology Branch Meeting, Christchurch, New Zealand

Paper Presentation, "Bacterial Subretinal Abscess: Successful Management with Extensive Retinectomy and Intravitreal Antibiotics" at the VIth Aegean Retina Meeting, Corfu, Greece

Course Director, Nantucket Retina

Invited Speaker, "New Approaches to the Diagnosis and Management of Endophthalmitis", "Advances in Vitreoretinal Surgery for Diabetic Traction Detachment" XXXth Congresso Brasileiro de Oftalmologia, Recife, Brazil

Faculty, "Challenges in Endophthalmitis Management and Treatment", "Management of Diabetic Traction Retinal Detachment" 1st Retina-Macula-Vitreous Hippocratic Symposium, Athens, Greece

Faculty "New Experience with Rehabilitation of Hypotonous Eyes" Vitreoretinal Update 1999, sponsored by the American Academy of Ophthalmology, Orlando, FL

Faculty, Course 472 "Suddenly Everything Was Going Better AFTER...a.k.a.Everything Was Going Just Fine UNTIL...", American Academy of Ophthalmology Annual Meeting, Orlando, FL

Invited Lecture, "Septic Retinitis", Infectious Diseases of the Choroid and Retina Symposium, sponsored by the American Academy of Ophthalmology, Orlando, FL

Visiting Professor, Wills Eye Hospital, Philadelphia, PA

Invited Speaker, "Retinal Vascular Occlusions", New England Ophthalmological Society, Boston MA

Paper Presentation, "Vitreoretinal Surgery in Association with Permanent Keratoprosthesis" at the 32nd Annual Meeting of the Retina Society, Maui HI

2000

Faculty, New Treatments for Neovascular Age-related Macular Degeneration, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Cambridge MA

Invited Speaker, "Therapeutic Algorithm for Postoperative Endophthalmitis", 3rd International Symposium on Ocular Pharmacology and Pharmaceutics, Lisbon, Portugal

Program Chairman, Aspen Retinal Detachment Society

Faculty, "Subretinal Surgery and Retinal Translocation for CNV in AMD" First International Course on Photodynamic Therapy, Lausanne Switzerland

Invited Speaker, Nuevos Avances en el Diagnóstico y Tratamiento Quirúrgico en Oftalmología, Barcelona, Spain

Invited Lecturer, "Research Toward Improved Management of Retinal Vascular Occlusions" at the 33rd Panhellenic Ophthalmological Congress, Thessaloniki, Greece

Invited Speaker, "Surgery for Choroidal Neovascularization I: Subretinal Membrane Excision and Hemorrhage Removal" New England Ophthalmological Society, Boston, MA

Course Director, Nantucket Retina

Invited Speaker, "The Diabetic Retinopathy Vitrectomy Study (DRVS): Lessons From a Forgotten Trial", "New Technologies for Vitrectomy for Diabetic Traction Detachment: Lasers for Tissue Transection and Removal, Enzymes, Glues, Biological patches, and Drug Delivery Systems" DR 2000: International Forum on Diabetic Retinopathy, Naples, Italy

Paper presentation, "Current Results with Vitreoretinal Surgery in Eyes with a Permanent Keratoprosthesis" for the XXIIInd meeting of the Club Jules Gonin, Taormina, Italy

Invited Speaker, Oregon Ophthalmological Alumni Association, 55th Annual Meeting, Casey Eye Institute, Portland OR

Paper Presentation, "Subfoveal Surgery without Hyaloid Removal in Younger Patients" at the 33rd Annual Meeting of the Retina Society, Coral Gables FL

Invited Lecture, "Virulence Factors: Implications for Treatment of Endophthalmitis" Retina 2000: Management of Posterior Segment Disease, sponsored by the American Academy of Ophthalmology, Dallas, TX

Invited Speaker, “Vitreotomy: How To Begin; Case Selection, Techniques, and Postoperative Care” for the Department of Ophthalmology, Udine, Italy

Invited Lecture, “Chirurgia della Macula” (Macular Surgery, given in Italian) for the Societa Italian della Retina, Settimana Oftalmologica Italiana, Naples, Italy

Invited Lecture, “Macular Surgery” for the Connecticut Retina Association, Waterbury, CT

2001

Invited Speaker, the Second International Retina and Vitreous Symposium of the Egyptian Vitreoretinal Society, Sharm El-Sheikh, Egypt

Program Chairman, Aspen Retinal Detachment Society

Invited Speaker, “Unsheathing of Arteriovenous Crossings in Branch Retinal Vein Occlusion” in Options, Controversies, And New Developments in Vitreoretinal Diseases and Surgery, Cole Eye Institute of the Cleveland Clinic, Cleveland OH

Invited Lecture “Perspectives on the Surgical Treatment of Macular Degeneration” (given in Italian) for Macula A Torino, Turin, Italy

Invited Speaker “Sub-Tenon’s Retrobulbar Anecortave Acetate With and Without Visudyne PDT in Patients with Subfoveal Age-Related Macular Degeneration (AMD)—Clinical Safety Profile;” “Laser in Vitreoretinal Surgery;” “Surgical Management of Branch Retinal Vein Occlusion;” “Management of Retinal Detachment in Highly Myopic Eyes;” “Surgical Ablation of Myopic Choroidal Neovascularization;” “Postoperative Endophthalmitis: Prognosis, Prophylaxis, and Treatment” at the XIIIth Congress of the European Society of Ophthalmology, Istanbul, Turkey

Invited Lecture “Postoperative Endophthalmitis: Diagnosis, Prophylaxis, and Treatment” (given in Italian) for the Italiani D’America Society, Pesaro, Italy

Invited Speaker “Diabetic Macular Edema: Surgical Treatment;” “Surgery for Retinal Vein Occlusion” (both given in Italian) for Advances in Macular Diseases, Gubbio, Italy

Paper Presentation, “Lamina Cribosa Surgery for Central Retinal Vein Occlusion” for the VIIth Aegean Retina Meeting, Crete, Greece

Course Director, Nantucket Retina

Invited Speaker, "Post Cataract Endophthalmitis", New England
Ophthalmological Society, Boston, MA

Faculty, Moderator for a Panel on Macular Surgery, Retina 2001: A Retina
Odyssey, sponsored by the American Academy of Ophthalmology Annual
Meeting, New Orleans, LA

Invited Lectures, "The Latest in Vein Occlusion", "Pars Plana Vitrectomy for
Diabetic Macular Traction Detachment" the American Academy of
Ophthalmology Annual Meeting, New Orleans, LA

2002

Invited Speaker, "Vitrectomy for Diabetic Traction Detachment,"
"Surgical Treatment for Retinal Vascular Occlusions," and
"Macular Hole Surgery and ILM Peeling with ICG" at the
Course on Vitreoretinal Diseases, Asociacion para Evitar la
Ceguera en Mexico, Mexico City, Mexico

Moderator of Panel "Endophthalmitis/Posterior Segment Complications of
Anterior Segment Surgery" at the 40th Anniversary Scientific Meeting of the
Bascom Palmer Eye Institute, Miami FL

Program Chairman and Faculty, Aspen Retinal Detachment Society

Invited Speaker, "Surgical Removal of Subretinal Membranes;" Lead Moderator
for Live Vitreoretinal Surgery, and Panel "Vitreoretinal Surgery for Diabetic
Retinopathy" Frankfurt Retina Meeting 2002, Frankfurt, Germany

Invited Faculty, "Surgical Approaches to Choroidal Neovascularization,"
"Endophthalmitis", "Laser Therapy for Diabetic Macular Edema," and
"Experimental Therapies for Vein Occlusions" for 74th Annual Spring
Postgraduate Conference, Current Concepts in Macular and Vitreoretinal
Diseases, University of Michigan Kellogg Eye Institute, Ann Arbor, MI

Invited Lecture, "Advances in Laser Technology for Vitreoretinal Diseases,"
Harvard Medical School Department of Ophthalmology Biennial Research
Retreat, Boston, MA

Invited Lectures, “New Observations Regarding Surgery for Macular Edema Due to Diabetic Retinopathy, Central Retinal Vein Occlusion, and Pseudophakic CME,” and “Surgery for Retinal Venous Occlusions: Experimental Approaches and Clinical Experience,” (both given in Italian), Macula a Torino, Turin, Italy

Invited Lecture “Unusual Indications in the Use of Intraocular Perfluorochemicals and Tamponades” (given in Italian) at Endotamponades and Intraocular Substances in Vitreoretinal Surgery, Ravenna, Italy

Course Director, Nantucket Retina

Paper presentation, “Lamina Puncture for Central Retinal Vein Occlusion: Initial Experience in Patients”, for the XXIVth meeting of the Club Jules Gonin, Vougliameni, Athens, Greece

Faculty, Moderator for Panel on Retinal Venous Occlusive Disease, Retina 2002: Giant Steps: A Look to the Past—An Eye on the Future, sponsored by the American Academy of Ophthalmology Annual Meeting, Orlando FL

Invited Moderator for “Macular Surgery” Panel for the American Academy of Ophthalmology Annual Meeting, Orlando, FL

2003

Invited Lecture “Post-surgical Endophthalmitis: Diagnosis and Treatment” (given in Italian) at Hospital San Raffaele, Milan, Italy

Invited Lecture “Anecortave Acetate in Age-related Macular Degeneration: Clinical Results” (given in Italian) at Societa' Italiana Laser in Oftalmologia XIXth meeting, Cortina, Italy

Program Chairman, Aspen Retinal Detachment Society

Faculty, Panel on Surgery for Retinal Vascular Occlusions, New England Ophthalmological Society, Boston, MA

Invited Faculty, “Vitreoretinal Surgery In Association With Permanent Keratoprosthesis Placement,” “Lamina Puncture For Central Retinal Vein Occlusion,” “Submacular Surgery In Patients Aged 55 Or Younger,” Jules Stein Eye Institute Annual Postgraduate Seminar, Los Angeles, CA

Invited Faculty, "Diabetic Traction/Rhegmatogenous Retinal Detachment,"
"Venous Occlusive Disease," and "Vitreoretinal Surgery In Association With
Permanent Keratoprosthesis Placement," Bascom Palmer Eye Institute 2003
Vitreoretinal Course, Miami FL

Invited Faculty, "Anacortave Acetate for Age-related Macula Degeneration"
Alcon Impact Meeting, Venice, Italy

Invited Lecture, "Advances in Vitreoretinal Surgery for Retinal Venous
Occlusions," for the Annual Meeting of the Societe Francaise d'Ophtalmologie,
Paris, France

Invited Lecture "Retinal Surgery In Association with Permanent
Keratoprosthesis" (given in Italian) at Retina in Progress: Present and Future,
Milan, Italy

Invited Lectures "Surgical Therapy of Retinal Vein Occlusions" and "New
Frontiers in Vitreoretinal Surgery" (both given in Italian) and Chairman, Live
Surgery session at the 5th GIVRE meeting, Reggio Calabria, Italy

Course Director, Nantucket Retina

Invited Lecture "Myopia and Giant Retinal Tear" (given in Italian) for the sixth
international congress of the Fondazione G.B. Bietti, Rome, Italy

Paper Presentation, "Lamina Puncture for Central Retinal Vein Occlusion:
Preliminary Results of a Pilot Study" at the 36th Annual Meeting of the Retina
Society, Chicago IL

Faculty "25 Gauge Vitrectomy: A Passing Fad" The Retina Debates 2003; New
Technology and Controversies from the Posterior Segment, sponsored by the
American Academy of Ophthalmology Annual Meeting, Anaheim CA

Invited Lectures "Vitreoretinal Surgery in Association with Permanent
Keratoprosthesis" and "Lamina Puncture for Central Retinal Vein Occlusion" for
Ophthalmology 2004 Meeting, UCSF, San Francisco CA

2004

Invited Faculty, "Optical Coherence Tomography: The State of the Art", the
Wilmer Ophthalmological Institute, Baltimore MD

Invited Lecture, "Current Insights on the Pathogenesis of Proliferative Retinopathy, Current Pharmacologic Therapy, and Timing and Indications for Surgical Intervention", (given in Italian), for Controversies in Vitreoretinal Surgery, Treviso, Italy

Invited Lectures, "Surgical Excision of Subretinal Neovascular Membranes: Current Indications, Technique, and Results", and "Lamina Puncture for Central Retinal Vein Occlusion" (both given in Italian), for Vitrectomy in Vascular Diseases of the Choroid and Retina, Niguarda Hospital, Milan Italy

Program Chairman and Faculty, Aspen Retinal Detachment Society

Invited Lectures, "Diabetic Retinopathy: Advances in Pathophysiology and Treatment", and "New Experimental and Clinical Approaches to Retinal Vascular Occlusions" for Technology to Trends, L.V. Prasad Eye Institute, Hyderabad, India

Invited Faculty, Lead Moderator for Live Vitreoretinal Surgery, Frankfurt Retina Meeting 2004, Frankfurt, Germany

Invited Lectures, "Overview of Treatments for Age-related Macular Degeneration", "Anecortave Acetate for Age-related Macular Degeneration: 24 Month Results", "Potential for Systemic Therapy of Macular Edema", "Sheathotomy for Branch Retinal Vein Occlusion", and "Lamina Puncture for Central Retinal Vein Occlusion", (all given in Italian) for New Therapies in Retinal Diseases, Rome, Italy

Invited Lecture "Surgical Management of Dislocated and Secondary IOLs" (given in Italian) for Italiani D'America, Cervia, Italy

Invited Lectures, "Proliferative Diabetic Retinopathy: Pathophysiology and Treatment", and "Retaane (Anacortave Acetate) Juxtapapillary Injection for Age-related Macular Degeneration with Choroidal Neovascularization: Two-year Efficacy and Safety Results" for the 3rd Retina-Macula-Vitreous Hippocratic Symposium, Thessaloniki, Greece

Invited Faculty, "Surgical Excision of Subfoveal Choroidal Neovascularization", and "Anacortave Acetate for Age-related Macular Degeneration: 24 Month Results", for the 37th Panhellenic Ophthalmologic Congress, Porto Carras, Greece

Course Director, Nantucket Retina

Invited Lecture, "Antioxidants and Zinc for Certain Cases of AMD, as Suggested by AREDS" (given in Italian) for Prevention of Progression of AMD, Fondazione Bietti, Rome, Italy.

Paper Presentation, "Safety of the VEGF 165 Antagonist, Macugen, in AMD: Findings of the V.I.S.I.O.N. Trials" at the 37th Annual Meeting of the Retina Society, Baltimore MD

Faculty, Panel Moderator "When You Thought Things Couldn't Get Worse" for Everything You Wanted To Know About The Retina, sponsored by the American Academy of Ophthalmology, New Orleans, LA

Invited Lecture, 'Posterior Juxtapapillary Pharmacotherapy for AMD' for the annual meeting of the American Academy of Ophthalmology, New Orleans, LA

Invited Lectures, "Leading Edge Developments in the Medical and Surgical Treatment of Vitreoretinal Diseases", "Retinal Vascular Surgery: Clinical Applications and Current Research", and "The Pathophysiology of the Proliferative Retinopathies" for the 18th Visiting Retina Lecture, Kapi'olani Medical Center at Pali Momi, Honolulu, Hawaii

2005

Invited Lectures, "Advances in the Management of Age-related Macular Degeneration", "Leading Edge Developments in Vitreoretinal Surgery", "Medical Retina: A Course for Specialists", "Surgical Retina: A Course for Specialists" for the 75th Annual Meeting of the Ophthalmological Society of South Africa, Cape Town, South Africa

Invited Lecture, "Current Status of Vitreoretinal Surgery in the Management of Age-related Macular Degeneration", (given in Italian) for Advances in AMD, Fermo, Italy

Invited Lecture, "Advances in Technology for Vitreoretinal Surgery in the Last Twenty Years" (given in Italian) for the Società Oftalmologica Triveneta, Treviso, Italy

Paper presentation, "Second Year Efficacy Data From the VISION Study" at the 28th Annual Macula Society meeting, Key Biscayne FL.

Invited Lectures, "Current Status of Retane", and "Advances in Vitrectomy Techniques and Instrumentation" (both given in Italian) for Retina In Progress, Milan, Italy

Invited Lecture, "Emerging Treatments for Macular Degeneration" for the Virginia Society of Ophthalmology 22nd Annual Meeting, the Homestead, Hot Springs, VA

Paper Presentation, "Results of the Second Year of Macugen for the Treatment of Neovascular AMD (V.I.S.I.O.N.), 23rd Annual Meeting of the American Society of Retinal Specialists, Montreal, Canada

Paper Presentation, "Intravitreal Steroid Therapy: A Critical Evaluation of Clinical Experience and Basic Research" at the IXth Aegean Retina Meeting, Crete, Greece

Course Director, Nantucket Retina

Paper Presentation, "The V.I.S.I.O.N. Study: Results of Exploratory Subgroup Analyses" at the 38th Annual Meeting of the Retina Society, Coronado CA

Faculty "The Role of Transvitreal Optic Nerve Surgery for Central Retinal Vein Occlusion in 2005" Retina 2005: Changing Concepts and Controversies, sponsored by the American Academy of Ophthalmology, Chicago, IL

Invited Lecture, "Leading Edge Advances in Vitreoretinal Diseases: for the New York Academy of Medicine, New York, NY

Invited Lecture, "Vitreoretinal Surgery with 25 Gauge Technology: Experience at a Tertiary Referral Center," New England Ophthalmological Society, Boston, MA

2006

Invited Lecture, "Evolutionary and Revolutionary Trends in Vitreoretinal Surgery" given at Macula 2006, New York, NY

Faculty, "Macugen: Subgroup Analyses, Second Year Data, DME Results", "Intravitreal Steroid Therapy: A Clinical and Basic Science Perspective", "Changing Approaches in Vitreoretinal Surgery for Primary and Complicated Retinal Detachment", "Observations on the Management of Dislocated and

Secondary IOLs: A Vitreoretinal Surgeon's Perspective", "Ocular Rehabilitation with Vitreoretinal Surgery with Permanent Keratoprosthesis", Retina Section of Hawaiian Eye 2006, Maui, HI

Paper Presentation, "Lamina Puncture for Central Retinal Vein Occlusion", Annual Meeting of the Macula Society, San Diego CA

Program Co-chairman and Faculty, Aspen Retinal Detachment Society

Visiting Professor, University of Louisville, Louisville, KY; Invited Lecture, "Neovascular AMD: Advances in Diagnosis and Therapy" for the Louisville Academy of Ophthalmology

Invited Faculty, Lead Moderator for Live Vitreoretinal Surgery, Frankfurt Retina Meeting 2006, Frankfurt, Germany

Invited Lecture, "Age-related Macular Degeneration: Advances in Diagnosis and Management", the 3rd Annual Robert Haimovici Lecture, Boston University Medical School, Boston, MA

Invited Lectures, "Evolutionary and Revolutionary Trends in Vitreoretinal Surgery", "Advances in Age-related Macular Degeneration", and "Treatment of Retinal Vascular Occlusions", Yale Spring Symposium/Alumni Day, New Haven, CT

Invited Lecture, "Vitreoretinal Surgery for Retinal Vascular Occlusions" Cours Inaugural De l'Hôpital Ophtalmique Jules-Gonin, Lausanne, Switzerland

Course Director, Nantucket Retina

Invited Lectures, "Vitreoretinal Surgery: Evolutionary and Revolutionary Trends", "The Use of Anti-VEGF Drugs for Diabetic Macular Edema" (both given in Italian) for New Therapies in Retinal Diseases 2006, Rome, Italy

Paper Presentation, Vitreoretinal Surgery for Posterior Segment Complications in Eyes with Permanent Keratoprosthesis, at the combined meeting of the Club Jules Gonin and the Retina Society, Cape Town, South Africa

Faculty, Moderator of Panel on Small Gauge (23, 25) vs. 20 Gauge, Retina 2006: Emerging New Concepts, sponsored by the American Academy of Ophthalmology, Las Vegas NV

Invited Lecture “Lamina Puncture and Radial Optic Neurotomy for Central Retinal Vein Occlusion” for the annual meeting of the American Academy of Ophthalmology, Las Vegas NV

Invited Lecture “Diabetic Retinopathy: Advances in Pathophysiology, Drug Treatment, and Vitreoretinal Surgery” for the Paul J. Schupf Invitational Symposium, Lighthouse International, New York, NY

Invited Lectures “Buckle Surgery vs. Primary Vitrectomy: Is There Still A Role For Scleral Buckling?” and “Anti – VEGF 4: Critical comparisons of study results and case series: *Pegaptanib* – *Ranibizumab* – *Bevacizumab*” for Retina Summit, Karlsruhe, Germany

2007

Invited Speaker, “Progress (and Lack of Progress) in the Management of Retinal Venous Occlusions”, Grand Rounds, Harkness Eye Institute, Columbia University, New York NY

Faculty, “Retinal Disease Management 2010”, Columbia University 2007 Basic Science Course in Ophthalmology, New York NY

Faculty, “Evolutionary and Revolutionary Trends in Vitreoretinal Surgery”, 35th Aspen Retinal Detachment Society Meeting, Snowmass CO

Invited Speaker, Endocrinology Grand Rounds, Weill Cornell Medical College, New York NY

Invited Lecture “Maculopathy Update” (given in Italian) for the Societa Oftalmologica Italiana 5th International Congress, Rome, Italy

Paper Presentation, “Minimalist Strategies for Treating AMD” at the Xth Aegean Retina Meeting, Rhodes, Greece

Course Director, Nantucket Retina

Invited Speaker, “Weill Cornell Department of Ophthalmology: Organization for Patient Care, Research, and Education”, Attualita e Prospettive della Ricerca in Oftalmologia” Centenario della Nascita del Prof G. B. Bietti, Fondazione Bietti, Rome, Italy

Invited Moderator, "Micro Incision Vitrectomy: A Paradigm Shift in Modern Vitreoretinal Surgery" European Vitreoretinal Society Symposium, Venice, Italy

Paper Presentation, "Changing Trends in Retinal Detachment Surgery: Complex Choices for Surgeons, Patients, and Physicians-in-Training" at the 40th Annual Meeting of the Retina Society, Boston MA

Invited Speaker, "Changing Trends in Vitreoretinal Surgery" Grand Rounds, Department of Ophthalmology, New York Medical College, Valhalla NY

Invited Faculty, "Innovations in Surgical Therapy for Diabetic Retinopathy", "Fluids and Gases in Advanced Techniques", "Kenalog, ICG & Methylene Blue: The Good, the Bad and the Ugly", The Ocular Immunology & Uveitis Foundation's Second Annual Physician Education Conference: What's New in Posterior Segment Disorders, Boston MA

Faculty, "Next Generation Targets for AMD Therapy: Beyond VEGF Inhibitors", and "Surgical Treatments for Central and Branch Retinal Vein Occlusion: Is There a Role?" Retina 2007: A View to the Future, sponsored by the American Academy of Ophthalmology, New Orleans LA

2008

Faculty, "Lasers in Ophthalmology", Columbia University 2008 Basic Science Course in Ophthalmology, New York NY

Visiting Professorship in honor of Victor T. Curtin, MD, Lectures: "Advances in the Management of Retinal Vascular Occlusions", "Diabetic Retinopathy: Pathophysiology, Laser Therapy, Pharmacologic Treatment, and Vitreoretinal Surgery," "Retinal Lasers", "Neovascular Age-related Macular Degeneration", Bascom Palmer Eye Institute, University of Miami, Miami FL

Invited Faculty, 60th Annual Wills Eye Institute Alumni Conference, 1) "Retinal Detachment Surgery: Personal Preferences and General Trends", and 2) "A Minimalist Approach to the Treatment of Age-related Macular Degeneration" Philadelphia, PA

Program Co-chairman, 37th Aspen Retinal Detachment Society

Invited Speaker, University of Medicine and Dentistry of New Jersey Grand Rounds, "Evolutionary and Revolutionary Trends in Vitreoretinal Surgery" Newark NJ

Invited Faculty, Illinois Eye Review, "Diabetic Retinopathy", "Current Trends in Vitreoretinal Surgery", "Age-related Macular Degeneration", "Retinal Lasers", "Advances in the Management of Retinal Venous Occlusions" University of Illinois, Chicago IL

Invited Speaker, Albert Einstein College of Medicine, Montefiore Medical Center, "Evolutionary and Revolutionary Trends in Vitreoretinal Surgery" Bronx NY

Invited Faculty, 5th Retina-Macula-Vitreous Hippocratic Meeting, "Advances in Lasers for Retinal Photocoagulation", "Retinal Detachment Surgery: Personal Preferences and General Trends", and "Next Generation Targets for AMD Therapy: Beyond VEGF Inhibitors" Aristotle University, Thessaloniki Greece

Invited Faculty, Lead Moderator for Live Vitreoretinal Surgery, Frankfurt Retina Meeting 2008, Frankfurt, Germany

Moderator and Co-Organizer, Retina Society Update in Diabetic Retinopathy, World Ophthalmology Congress 2008, Hong Kong

Invited Faculty, Clinical Low Vision: East Meets West, "Macular Degeneration, Diabetic Retinopathy, and Permanent Keratoprosthesis: New Treatments and Outcomes", World Ophthalmology Congress 2008, Hong Kong

Course Director, Nantucket Retina

Paper Presentation, "Progress in Vitreoretinal Surgery for Issues Associated with Permanent Keratoprosthesis" at the XXVIth Meeting of the Club Jules Gonin, St. Moritz, Switzerland

Invited Lecture, "Vitreoretinal Surgery in Diabetes" for Fermo...Occhio e Diabete, Fermo, Italy

Paper Presentation, "A Combination Strategy for AMD Targeting Platelet-derived Growth Factor (PDGF): Preliminary Results from a Phase 1 Trial Evaluating the Enhancement of Anti-VEGF Effect via Pericyte Stripping by Anti-PDGF Therapy" at the 41st Annual Meeting of the Retina Society, Scottsdale AZ

Moderator, Session XIII, Occlusive Vascular Disease and Macular Diseases, Retina Subspecialty Day "Vistas and Viewpoints"; Moderator, Academy Café Retina Session at the American Academy of Ophthalmology, Atlanta GA

2009

Faculty, "The Management of Primary Retinal Detachment", Columbia University
2009 Basic Science Course in Ophthalmology, New York NY

Visiting Professor and invited lecture "Controversies in the Management of
Primary Retinal Detachment," New York Eye and Ear Infirmary, the New York
Medical College, New York, NY

Paper Presentation, "Complicated Retinal Detachment with Permanent
Keratoprosthesis", Macula 2009, New York NY

Invited Lectures, "Observations on the Management of Retinal Detachment",
"Diabetic Retinopathy: Current Challenges and New Treatment Strategies" for
the Illinois Association of Ophthalmology/Chicago Ophthalmological Society
Combined Annual Meeting, Rosemont IL

Program Co-chairman, 38th Aspen Retinal Detachment Society

Invited Faculty, "Techniques in the Repair of Giant Tears", "Vitreoretinal Surgery
and Permanent Keratoprosthesis", "Continued Challenges in Diabetic
Vitreectomy", "Practical Guidelines for Intravitreal Injections", "Selection of
Operation for Primary Retinal Detachment", "Mixed Gauge Vitreoretinal
Surgery", 10th Antwerp Vitreoretinal Course, Antwerp Belgium

Invited Faculty, "Tips and Tricks for Microincision Surgery", Retina Summit
Karlsruhe 2009, Karlsruhe Germany

Invited Faculty, "The Future of Diabetic Retinopathy Treatment", Yale Retina
2009, New York NY

Invited Lecture, "Advances in the Management of Diabetic Retinopathy", Hamad
Hospital, Doha, Qatar

Visiting Surgeon, Subramaniam Bharati Eye Centre (Moka Eye Hospital), Moka
Mauritius

Invited Lectures, "Challenges in the Surgical Management of Diabetic
Retinopathy", "Current Trends in Retinal Detachment Repair" Current
Concepts in Ophthalmology, Instituto Universitario Barraquer, Barcelona Spain

Invited Lectures, "Ophthalmic Lasers: A Look At What's Inside the Box, How it Works, and Why It Matters to the Treating Physician" Department of Ophthalmology, University of Texas, and "Diabetic Retinopathy: Advances in Pathophysiology, Diagnosis, Laser Treatment, Medical Therapy and Vitreoretinal Surgery" Department of Ophthalmology, Baylor College of Medicine, Houston TX

Paper Presentation, "Management of Retinal Detachment: Recent Trends and Personal Preferences" Weill Cornell Ophthalmology Department Alumni Day, New York NY

Course Co-director, and paper presentations "Vasoproliferative Tumor of the Retina After Scleral Buckling Surgery" and "Controversies in the Management of Primary Retinal Detachment" for Aegean Retina XI, Chania, Crete, Greece

Course Director, Nantucket Retina

Faculty, European School for Advanced Studies in Ophthalmology (ESASO), Retinal Detachment, and Retinal Venous Occlusions, Lugano, Switzerland

Invited Lecture, "Is Sutureless Vitrectomy the Better Vitrectomy?" 4th International Conference on Vitreoretinal Disease, Vienna, Austria

Paper Presentation, "Anti-VEGF Gene Therapy for Ocular Neovascularization Using an Adeno-associated Virus Gene Transfer Vector Encoding the Murine Equivalent of Bevacizumab" at the Retina Congress 2009, New York NY

Panel Member, Diabetic Vitrectomy, Retina Subspecialty Day; Moderator, Academy Café Retina Session; Paper Presentation "Applicability of 23- and 25-Gauge Instrumentation to Anterior Segment Surgical Issues" and Symposium Organizer and Co-Moderator: "Advances in Diagnostic and Surgical Technology for Retinal Disease: A Symposium for the General Ophthalmologist" at the American Academy of Ophthalmology, San Francisco CA

2010

Faculty, "The Management of Primary Retinal Detachment", Columbia University 2010 Basic Science Course in Ophthalmology, New York NY

Invited Lecture, "Management of Endophthalmitis; What Have We Learned 15 Years After the Endophthalmitis Vitrectomy Study (EVS)?" at Macula 2010, The Wilmer Eye Institute of the Johns Hopkins University School of Medicine, Baltimore MD

Host Lecture, "The Improving Landscape for Visual Rehabilitation with Permanent Keratoprosthesis" for the 1142nd Meeting of the New York Ophthalmological Society, New York, NY

Invited Lecture, "Vitreoretinal Surgery for Diabetic Retinopathy" for the Greater New York Ophthalmology Clinical Lecture Series, New York NY

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery; Lecture, "A Minimalist Approach to AMD Therapy", Frankfurt Retina Meeting 2010, Frankfurt, Germany

Program Chairman, 39th Aspen Retinal Detachment Society

Invited Faculty, Illinois Eye Review, "Diabetic Retinopathy", "Management of Primary Retinal Detachment", and "Age-related Macular Degeneration", University of Illinois, Chicago IL

Invited Lecture, "Development of an Erbium-YAG Laser for Vitreoretinal Surgery" for Progress Comes From Doing the Unconventional, a memorial meeting in honor of Robert Machemer, MD, Durham NC

Co-Chair and Moderator, Symposia "What's New On Management of Retinal Disease", "Surgical Management of Macular Diseases", and "Advances in Instrumentation and Adjuvant Pharmacology for Vitreoretinal Surgery" for the World Ophthalmology Congress 2010, Berlin Germany

Invited Lectures, "Advances in the Evaluation and Management of Retinal Detachment", "A Minimalist Approach to AMD Management", and "Personal Preferences in Small Gauge Vitrectomy", Masters in Ophthalmology 2010, Florida Society of Ophthalmology, Orlando FL

Faculty, First Annual Fellows Course in Vitreoretinal Surgery, "Vitrectomy for PVR", "Vitrectomy for PDR", Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

Course Director, Nantucket Retina

Invited Lecture "Myopia and Retinal Detachment" (given in Italian) for Fermo...Myopia a 360°, Fermo, Italy

Paper Presentation, "Mixed Gauge Vitrectomy: A Practical Approach with Evolving Technology" at the Retina Society 43rd Annual Meeting, San Francisco CA

Moderator, Vitreoretinal Surgery: Part 1, at Retina 2010: A Panretinal Perspective, Chicago IL

Moderator, Panel discussion on the Management of Primary Rhegmatogenous Retinal Detachment, American Academy of Ophthalmology, Chicago IL

Paper Presentation, "Advances in Vitreoretinal Surgery in Eyes with Permanent Keratoprosthesis" at the XXVIIth Meeting of the Club Jules Gonin, Kyoto, Japan

Keynote Lecture, "Principles in the Diagnosis and Management of Traumatic Retinal Detachment" and invited lectures "Management of Post Traumatic Choroidal Hemorrhage and Retinal Detachment" and "Treatment of Endophthalmitis" at the 2nd Qatari Ophthalmology Conference on Ocular Trauma, Doha, Qatar

2011

Invited Lecture "The Practice of Retina 2011", Columbia University 2011 Basic Science Course in Ophthalmology, New York NY

Invited Lecture "Management of Primary Retinal Detachment", Kilimanjaro Christian Medical Center, Kilimanjaro, Tanzania

Presentation "It's Here, I Love it, and I'm Never Going Back" for symposium on electronic medical records at the AUPO meeting, Phoenix AZ

Invited Faculty, Illinois Eye Review, "Diabetic Retinopathy", "Management of Primary Retinal Detachment", "Ophthalmic Lasers", "Gases and Tamponades in Vitreoretinal Surgery", "Stains and Colorants", "Endophthalmitis", and "Age-related Macular Degeneration", University of Illinois, Chicago IL

Session Moderator and Invited Lecture "ILM Peeling for Macular Edema" for Club Jules Gonin Symposium "Update in Macular Surgery" at the European Society of Ophthalmology (SOE) Meeting, Geneva, Switzerland

Faculty, European School for Advanced Studies in Ophthalmology (ESASO), The Management of Rhegmatogenous Retinal Detachment, Lugano, Switzerland

Invited Speaker, "Controversies in the Management of Retinal Detachment" for Annual Alumni Meeting, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston MA

Faculty, Second Annual Fellows Course in Vitreoretinal Surgery, "Vitreotomy for PVR", Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

Course Director, Nantucket Retina

Invited Surgeon and Participant, Millennium Villages Project Mbola Villages Cluster Ophthalmic Intervention, Tabora, Tanzania

Invited Participant, Moderator "From Bench to Bedside" Stanford University Byers Eye Institute Dedication, Palo Alto, CA

Moderator, Video Cases, and Presentation Co-author "Long-term Suppression of Ocular Neovascularization with a Single Intravitreal Administration of a Viral Gene Transfer Vector Coding for Bevacizumab" with S. Kiss (presenter) and R. Crystal; both at the 44th Retina Society Meeting, Rome, Italy

Panel Member, "Retinal Detachment Techniques"; Moderator, "The Great Debate", American Academy of Ophthalmology Annual Meeting, Orlando, FL

2012

Invited Lectures "Retinal Detachment Repair" and "Diabetic Retinopathy" at SUNY Downstate Medical Center Department of Ophthalmology Course "Current Concepts in Ophthalmology 2012", Atlantic City, NJ

Co-Moderator, Vitreoretinal Surgery Session at Macula 2012, New York, NY

Invited presentations "What I Missed Knowing" and "Finance and Administration of an EMR", and participant in "Symposium on Departmental Management" at the AUPO annual meeting, Miami, FL

Co-Moderator, Panel Discussion "Vitreoretinal Surgery: Surgical Techniques/Outcomes" at the Bascom Palmer Eye Institute 50th Anniversary Scientific Meeting "50 Years of Vision: Second to None", Miami, FL

Invited lecture, "Optic Nerve Surgery for CRVO; Is There A Role?"; Moderator, "Vascular Occlusion: New Treatments and Regimens, Including Surgery"; and Co-author "Ultra-Widefield Angiography in the Setting of Diabetes: Improving the Detection and Classification of Diabetic Retinopathy" with S. Kiss (presenter); all at the World Ophthalmology Congress 2012, Abu Dhabi

Program Co-chairman and Speaker, "Surgical Management of Severe Macular Edema", 40th Aspen Retinal Detachment Society

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery; Lecture, Frankfurt Retina Meeting 2012, Frankfurt, Germany

Invited Faculty, 5th Annual Illinois Eye Review, "Diabetic Retinopathy", "Management of Primary Retinal Detachment", "Ophthalmic Lasers", "Gases and Tamponades in Vitreoretinal Surgery", and "Age-related Macular Degeneration", University of Illinois, Chicago IL

Invited Speaker, "Mixed Gauge Vitrectomy", "ILM Peeling in Vitrectomy for Diabetic Macular Edema", "Management of Intractable Retinal Vein Occlusions", and "Medical and Surgical Management of Enhanced S Cone Syndrome" at the 27th APAO Meeting, Busan Korea

Invited Speaker, "Blindness Due to Retinal Diseases: Diabetic Retinopathy and Age-related Macular Degeneration" for a meeting entitled "Non-Sighted People: Master, I Want to See" sponsored by the Pontificio Consiglio per gli Operatori Sanitari, Fondazione "Il Buon Samaritano", Vatican City

Invited Speaker, "Retinal Detachment Surgery", 12th Meeting of the Croatian Ophthalmology Society, Bol, Island of Brac, Croatia

Faculty, Fourth Module for Surgical Retina, ESASO, Lugano, Switzerland

Meeting President and Speaker, "Internal Limiting Membrane Peeling for Chronic Macular Edema" at the XXVIIIth Meeting of the Club Jules Gonin, Reykjavik, Iceland

Faculty, Third Annual Fellows Course in Vitreoretinal Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA

Course Co-Director, Nantucket Retina

Faculty, Panel Moderator "Management of Retinal Detachment in 2012"; Panelist "Diabetic Retinopathy-Practical Management Issues", Retina Canada 2012, Niagara-on-the-Lake, Ontario, Canada

Moderator, Panel on Retinal Vascular Occlusions at "Retina 2012: The Winds of Change" at the retina subspecialty meeting of the American Academy of Ophthalmology, Chicago, IL

Invited speaker, "Advances in Ophthalmology: New Treatments from Medicine's Most Personalized Specialty" at the winter luncheon of Partners in Medicine, Weill Cornell Medical College and New York-Presbyterian

2013

Lead Moderator for Live Surgery Session and Invited Speaker, "Boston Keratoprosthesis" and "ILM Peeling in Severe CME: Does It Work?" for Present and Future Challenges in Severe Retinal Diseases, Verona, Italy

Program Co-Chairman, 41st Aspen Retinal Detachment Society, Snowmass CO

Co-Director, Seminar Week in Ophthalmology, American Austrian Foundation, Salzburg, Austria

Guest of Honor, Yale Ophthalmology Sixth Annual Resident's Research Day, Lectures "From Kilimanjaro to the Vatican: Observations on Global Health Initiatives in Ophthalmology", and Grand Rounds "The Management of Retinal Detachment: Advances, Challenges, and Controversies" New Haven CT

Invited Lecture, "Retinotomies and Retinectomies: Friend or Foe?" for the SOE 2013 European Congress of Ophthalmology, Copenhagen, Denmark

Faculty, Fifth Module 2013 for Surgical Retina, ESASO, Lugano, Switzerland

Invited Keynote Lecture, "Advances and Controversies in the Management of Primary Retinal Detachment" for the DOC 26th International Congress of German Ophthalmic Surgeons, Nuremberg, Germany

Presentation "Enhanced S-Cone Syndrome" Manhattan Ophthalmological Society, New York NY

Faculty, Fourth Annual Fellows Course in Vitreoretinal Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston MA

Course Co-Director, Nantucket Retina

Presentation "Why the 0.3 mg Dose of Ranibizumab Was Recommended for the Treatment of Diabetic Macular Edema"; Panelist, The Unplugged Symposium, both at the Annual Meeting of the American Society of Retina Specialists, Toronto Canada

Invited Lecture of Honor, "Progress in the Management of Retinal Detachment" (given in Italian) in the Aula Magna of the University of Catania, Catania, Sicily

Invited lecture, "Rhegmatogenous Retinal Detachment; Surgical Advances and Controversies" for the Symposium Scientifique en L'honneur du Professeur Leonidas Zografos, Geneva Switzerland

Invited Moderator, Fact or Fiction Panel at Retina Subspecialty Day "Let the Good Times Roll" at the Annual Meeting of the American Academy of Ophthalmology, New Orleans LA

Invited Moderator, Editors Panel, The Best of Retina, New York NY

Invited Participant, Expert Panel on Intravitreal Injection Technique and Monitoring, New York, NY

2014

Invited Lecture, "Why the 0.3 mg Dose of Ranibizumab was Recommended for the Treatment of Diabetic Macular Edema" for Macula 2014 Meeting, Wills Eye Hospital, Philadelphia PA

Invited Lecture, Diabetic and Hypertensive Retinopathy, Weill Bugando Medical Centre, Mwanza Tanzania

Program Co-Chairman, and Faculty lecture “Current Perspectives on Retinotomies and Retinectomies”, the 42nd Aspen Retinal Detachment Society, Snowmass CO

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery; Lecture: “Approaches to Retinotomies and Retinectomies”, Frankfurt Retina Meeting 2014, Frankfurt, Germany

Invited Lectures, “The Pericyte: A Novel Target (PDGF)”, and “Ranibizumab Update” for the WOC 2014 Meeting, Tokyo, Japan

Invited Lecture, “Retinotomy and Retinectomy: Changing Attitudes Toward an Indispensable Technique” for the 140th Anniversary Meeting, Department of Ophthalmology, University of Pennsylvania, Scheie Eye Institute, Philadelphia PA

Keynote Lecture, “Primary Retinal Detachment: Advances and Controversies” and invited lecture “Changing Trends in Retinotomy” for the Chicagoland Midwest Retina Update 4th Annual Meeting, Chicago IL

Grand Rounds Visiting Professor, “Controversies in the Management of Primary Retinal Detachment” and “Ophthalmic Lasers: A Look at What's in the Box, How It Works, and Why It Matters to the Laser Surgeon”, Scheie Eye Institute, University Of Pennsylvania, Philadelphia PA

Faculty, Fifth Module 2014 for Surgical Retina, ESASO, Lugano, Switzerland

Faculty, Fifth Annual Fellows Course in Vitreoretinal Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston MA

Presentation “Advances in Vitreoretinal Surgery in Association with Permanent Keratoprosthesis” at the XXIXth Meeting of the Club Jules Gonin, Zurich, Switzerland

Presentation “Advances in Vitreoretinal Evaluation and Surgery with Permanent Keratoprosthesis” at the 47th Retina Society Meeting, Philadelphia PA

Invited Speaker, “Management of Primary Retinal Detachment: Advances and Controversies”, “Options in the Treatment of Severe Macular Edema”, and “Permanent Keratoprosthesis: A Perspective for the General Ophthalmologist”

at the Annual Meeting of the New Jersey Academy of Ophthalmology, East Windsor NJ

Faculty, Retina Subspecialty Program “Retina 2014: Reaching New Heights”, and Invited Speaker, Young Ophthalmologists Meeting “It’s YO World, Jumpstart Your Career” at the Annual Meeting of the American Academy of Ophthalmology, Chicago IL.

Invited Faculty, 14th ESASO Retina Academy, Presentation “Anti-PDGF for AMD” and Moderator for Retinal Surgery Cases Panel

Moderator, Editor’s Choice Panel, Best of Retina 2014, New York NY

2015

Invited Keynote Lecture “Pathophysiology of the Vitreoretinal Interface” (given in Italian), Meeting Vitreo-retina Forever, Acquaviva delle fonti, Bari, Italy

Invited Lectures, "Traumatic Endophthalmitis: Diagnosis and Management", "Controversial Aspects in the Treatment of Primary Retinal Detachment", and "Current Perspectives on Retinotomy and Retinectomy for PVR Repair" at the 3rd Qatari Ophthalmology Conference, Doha Qatar

Lecture “From Kilimanjaro to the Vatican: Perspectives on Global Health Initiatives in Ophthalmology” The Century Association, New York NY

Program Co-Chairman, 43rd Aspen Retinal Detachment Society, Snowmass CO

Research Presentation “Investigating the Role of microRNAs in Retinal Disease,” The Shulsky Foundation Symposium, Miami FL

Invited Faculty, The Duke Advanced Vitreous Surgery Course 2015, “Current Use of Retinotomy in Retinal Detachment Repair”, “Tricks to Complicated Vitreoretinal Surgery with a Permanent Keratoprosthesis”, “Differences in Trends and Techniques in Vitreoretinal Surgery Between Europe and the United States”, Durham NC

Course Co-Director, Nantucket Retina

Invited Faculty, IX International Meeting, “Boston Keratoprosthesis and Vitreoretinal Surgery, Fondazione Bietti, Rome, Italy

Paper presentation “MicroRNAs in the Retina and Vitreous: New Targets for Diabetic Retinopathy”, The 48th Annual Meeting of the Retina Society, Paris, France

Faculty, Retina Subspecialty Program “Retina 2015: Upping the Ante at the Annual Meeting of the American Academy of Ophthalmology, Las Vegas, NV

Invited Faculty and Lead Moderator for Live Surgery, Floretina 2015, and talks: 1) Diabetic Retinal Complications After Cataract Surgery: Surgical indications, Prevention, and Management; 2) New Mininvasive Cutters and the Cutters of the Future; 3) ILM Peeling for Diabetic Macular Edema; 4) Permanent Keratoprosthesis and Vitreoretinal Surgery: New Approaches; 5) The Role of Relaxing Retinotomy in PVR, Florence, Italy

2016

Invited Lecture “Vitreotomy for Diabetic Macular Edema” (given in Italian), Meeting Vitreo-Retina Forever, Second Edition, Acquaviva delle fonti, Bari, Italy

Guest of Honor, 16th Retina Fellows’ Forum, Lecture “You can observe a lot just by watching”. Chicago, IL

Program Co-Chairman and Lectures “Different Preferences Between US and European Vitreoretinal Surgeons” and “Novel Management of Enhanced S-cone Syndrome”, 44th Aspen Retinal Detachment Society, Snowmass CO

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery, Frankfurt Retina Meeting 2016, Frankfurt, Germany

Invited Lectures “Global Health Initiatives: Observations by a Participant Late to the Game”, “Surgical Treatment of Severe Macular Edema”, and “Permanent Keratoprosthesis and Complex Ocular Reconstruction” at the Annual Convention of the Memphis Eye Society, Memphis TN

Paper presentation “MicroRNAs in the retina and vitreous as new targets for the treatment of vitreoretinal diseases” at the XXXth Meeting of the Club Jules Gonin, Bordeaux, France

Course Co-Director, Nantucket Retina

Faculty, Seventh Annual Fellows Course in Vitreoretinal Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston MA

Faculty, Retina Subspecialty Program “Retina: Winds of Innovation”, with talk “Giant Retinal Tear: Vitrectomy alone is sufficient” at the Annual Meeting of the American Academy of Ophthalmology, Chicago IL.

Invited Lecture “Determination of “Clinical Significance” in Neovascular Age-Related Macular Degeneration Randomized Clinical Trials: Lessons from Previous Clinical Trials and Statistical Considerations” at the 13th ISOPT Clinical Meeting, Rome Italy.

2017

Invited Faculty and Moderator for Panel “Diabetic Retinopathy: How would you manage these cases?” at Macula 2017, The Wilmer Eye Institute, John Hopkins Medical School, Baltimore MD

Invited Faculty, “Vitreotomy Timing in the Management of Retained Lens Fragments After Cataract Surgery” and “Management of Retinal Detachment with PVR: Vitrectomy Alone is Enough”; Lead Moderator for live surgery at VITREEX, /the Vitreoretinal Experience, Rovigo Italy

Grand Rounds, “Advances and Controversies in the Management of Primary Retinal Detachment”, Montefiore Medical Center, Bronx NY

Program Co-Chairman, 45th Aspen Retinal Detachment Society, Snowmass CO

Live Surgery Lead Moderator and Invited Faculty, The Vit/Buckle Society, Las Vegas NV

Live Surgery Lead Moderator and Invited Faculty, FLOREtina 2017, Florence, Italy

Invited Faculty and Lecture “Retinotomy and Retinectomy: Changing Trends” Mediterretina Club 2017, Parma, Italy

Paper presentation, XXXth Meeting of the Club Jules Gonin, Bordeaux France

Course Co-Director, Nantucket Retina

Faculty, Eighth Annual Fellows Course in Vitreoretinal Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston MA

Honoree as Past President at the 50th Annual Meeting of the Retina Society, Boston MA

Faculty, Retina Subspecialty Program “Retinal Mardi Gras” at the Annual Meeting of the American Academy of Ophthalmology, New Orleans LA

2018

Invited Lectures, “Re-Examination of the Role of Relaxing Retinotomy in PVR Detachment Repair” and “Differences in Vitreoretinal Surgery Approaches and Techniques Between Europe and the USA” for the XXIInd Congreso de la Sociedad Española de Retina y Vitreo, Santander, Spain

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery and talk “Relaxing Retinotomy in Complex Detachment Surgery”, Frankfurt Retina Meeting 2018, Frankfurt, Germany

Invited Keynote Lecture “Macular Surgery; New Diseases, New Techniques, and New Controversies” (“Chirurgia Della Macula; Nuove Patologie, Nuove Tecniche e Nuove Controversie”; given in Italian) at the IVth Meeting of Vitreoretina Forever, Nardo, Puglia, Italy

Course Co-Director, Nantucket Retina

Faculty, Ninth Annual Fellows Course in Vitreoretinal Surgery, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston MA

Invited Speaker, The Great Debate: “The Great Debate: Scleral Buckle is Better Than Vitrectomy For Primary Retinal Detachment Repair: CON” at the Annual Meeting of the American Academy of Ophthalmology, Chicago IL

Invited Speaker, New York Academy of Medicine, “Perspectives on a Career/Employment in an Academic Setting”, New York NY

Invited Faculty, “Current Perspectives on the Role of Relaxing Retinotomy in PVR Surgery” the 12th APVRS Meeting, Seoul S. Korea

2019

Invited Faculty, Case presentation Atlantic Coast Retinal Club, Panel member, Retinal Vascular Diseases, Macula 2019, Boston MA

Invited Faculty with Lecture “An Education-based Ophthalmology Program in Tanzania” at Global Neurosurgery 2019: A Practical Symposium, New York NY

Invited Speaker, “Pearls and Pitfalls: My Own Experiences With Mentors, Mentees, and Developing Faculty” and Panelist in a Symposium on Mentoring and Faculty Development at the 53rd Annual AUPO meeting, Ft. Lauderdale FL

Invited Speaker, “Things I Have Learned From Mentoring Faculty” at the Inaugural EnVision Ophthalmology Summit, Puerto Rico

Invited Speaker, “Advances and Controversies in the Management of Primary Retinal Detachment”, NYU Ophthalmology Grand Rounds, New York, NY

Program Co-Chairman, 47th Aspen Retinal Detachment Society, Snowmass CO

Invited Faculty with lectures “A Non-Hysterical Look at the Scleral Buckle Versus Vitrectomy Controversy for Primary RD”, “Surgery for DME: Failure is the Only Option”, “The Changing Role of Relaxing Retinotomy In Complex RD Repair”, “How to Approach Vitreoretinal Surgery in an Eye with a Keratoprosthesis”, and “Is Academic Medicine For You? What You Should Consider If You Are Interested and What I Look For in a Future Faculty Member”, Duke Advanced Vitreous Surgery Course and Fellows Course 2019, Durham NC

Invited Faculty with lectures “Unanswered Questions in Macular Surgery”, “Reevaluation of the Role of Relaxing Retinotomy in Complex Retinal Detachment Repair”, Surgical Treatment of Diabetic Macular Edema: Failure is the Only Option”, and “Differences in Surgical Approaches Between European and USA Vitreoretinal Surgeons” at Ophthalmology New Horizons, The 3rd Retina and Glaucoma Symposium, Lodz Poland

Invited Prior Bietti Medal Winner for Lecture “Nuovi Approcci Agli Interventi Vitreoretinici Negli Occhi Con Keratoprotesi Permanente” (given in Italian) at the 150th Annual Meeting of the Società Oftalmologica Italiana, Rome, Italy

Invited Faculty with Lectures “Vitrectomy for Diabetic Macular Edema: Failure Is the Only Option”, “Vitrectomy vs Scleral Buckling For Primary Retinal Detachment: Where Are We Today?” and Moderation of Live Surgery, FLORetina 2019, Florence Italy

Course Co-Director, Nantucket Retina

Faculty, Diabetic Retinopathy Panel, Retina Subspecialty Day at the American Academy of Ophthalmology Annual Meeting, San Francisco CA

2020

Invited Speaker with Lectures “Advances and Controversies in the Management of Primary Retinal Detachment” and “Navigating Treatment Options for Macular Edema” for the Washington Academy of Eye Physicians and Surgeons, and also Grand Rounds with Case Presentations and Lecture “Global Health Initiatives in Ophthalmology: Observations by a Participant Late to the Game”, University of Washington, Seattle WA

Moderator, Vitreoretinal Surgery Panel, Atlantic Coast Retina Club, New York, NY

Invited Speaker “Negotiating Skills” at the Envision Summit 2020, Puerto Rico

Program Co-Chairman, 48th Aspen Retinal Detachment Society, Snowmass CO

Invited Webinar Speaker “Permanent Keratoprosthesis 30 Years After Stevens-Johnson Syndrome” for Retinal Detachment: Surgical Treatment 360° FLORetina Virtual Educational Series.

Invited Lecture “Permanent Keratoprosthesis and Complex Ocular Reconstruction: New Opportunities and Challenges for the Vitreoretinal Surgeon” for the King Khaled Eye Specialist Hospital Global Virtual Lecture Series

Invited Presentation “Viscostretch: A Novel Surgical Technique For Repair of Large or Refractory Macular Holes” for the Virtual 32nd Meeting of the Club Jules Gonin

Session Co-Moderator “The Evolution of Vitreoretinal Surgery” for the Virtual 53rd Annual Meeting of the Retina Society

Invited Lecture “Unanswered Questions in Macular Surgery” for the Virtual “Retina in Linea Cincontinentes,” the 39th Annual Meeting of the Mexican Retina Association

Invited Lecture “The Role of Surgery for Diabetic Macular Edema (DME)” and panelist for OSN Virtual Meeting New York

Invited Late-Breaking Presentation “Avacincaptad Pegol, A Novel C5 Inhibitor, Significantly Reduces the Mean Rate of Geographic Atrophy Growth in the Phase 2/3 GATHER1 Clinical Trial” for the Virtual Annual Meeting of the American Academy of Ophthalmology

2021

Invited Co-Moderator Diabetic Retinopathy Panel, for the virtual MACULA 2021 meeting

Invited Faculty with lecture “Improving Ophthalmology Care in Tanzania; Successes, Challenges, and Lessons Learned” for the Cornell University S. C. Johnson College of Business Virtual Course “Global Perspectives in Healthcare”

Course Co-Director, Nantucket Retina

Invited Faculty with lecture “Unanswered Questions in Macular Surgery” in conjunction with the Bruner Lecture, Case Western Reserve University, Cleveland OH

Invited Faculty with lecture “Advances in Complex Ocular Reconstruction in Association with Permanent Boston (Dohlman) Keratoprosthesis” for Retina Subspecialty Day at the American Academy of Ophthalmology Annual Meeting, New Orleans LA

Invited Faculty with Lecture “Viscostretch: A Novel Technique For Large or Refractory Macular Holes” and Lead Moderator for Live Surgery, FLORetina 2021, Rome Italy

2022

Invited Moderator for Panel “The Future of AMD” for the MACULA 2022 meeting, Philadelphia PA

Invited Faculty with lecture “Advice for Cataract Surgeons from a Retina Perspective” for the Annual EnVision Summit, Fajardo Puerto Rico

Program Co-Chairman, 50th Aspen Retinal Detachment Society, Snowmass CO

Invited Faculty with Lecture “Surgical Elements of Wet AMD Treatment: The USEFUL, The IGNORED, and the RIGHTFULLY REJECTED” and participation in Panel “Vitreoretinal Surgery” at the 2022 meeting of the Pacific Retina Club, UCLA, Los Angeles CA.

Keynote Lecture “Unanswered Questions in Macular Surgery” and Lead Moderator for Live Surgery at Milano Retina 2022, Milan, Italy

Course Co-Director, Nantucket Retina

Moderator and Lecture in “Best of JVRD” session, and panelist “Vitreoretinal Surgery” at the annual meeting of the American Society of Retina Specialists 2022, New York NY

Invited Faculty with Lecture “Decision Making in Macular Hole Surgery: How To Select the Best Surgical Approach” and Lead Moderator for Live Surgery, FLORetina 2022, Rome Italy

2023

Invited Moderator for Panel “Innovative Approaches to Retinal Vascular Diseases” Panel Discussion for the MACULA 2023 meeting, Boston MA

Guest of Honor and the H. MacKenzie Freeman, MD Lecture “Turning Points in the Management of Giant Retinal Tear: The Transformational Insights and Surgical Approaches of H. MacKenzie Freeman, MD” and second lecture “Cataract Surgery Complications: Comments on PreOperative, IntraOperative, and PostOperative Management from a Retina Colleague” for the 791st meeting of the New England Ophthalmological Society, Boston MA

Invited Faculty with Lectures “Advances and Controversies in the Management of Primary Retinal Detachment” and “Unanswered Questions in Macular Surgery” for the Illinois Ophthalmology Review Course (virtual) 2023

Program Co-Chairman and Lecture “Turning Points in the Management of Giant Retinal Tear: A Historical Perspective on the Transformational Insights and Surgical Approaches of H. MacKenzie Freeman, MD” at the 51st Aspen Retinal Detachment Society, Snowmass CO

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery Session and Surgical Video Session, Frankfurt Retina Meeting 2023, Frankfurt, Germany

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery Session, and Lecture “New Complexity in Decisions Regarding Macular Hole Surgery” for the Vitreoretinal Experience (VitReEx) Meeting 2023, Venice, Italy

Invited Faculty and Lead Moderator for Live Vitreoretinal Surgery Sessions, and Moderator for session “European debate Retina battles: Management of primary retinal detachment” for the 23rd Congress on the Italian Society of Vitreoretinal Surgery GIVRE 2023, Trieste, Italy

Invited Faculty and Lead Moderator of Live Surgery; Co-Organizer of Symposium “State-of-the-Art Diagnosis and Management of Vitreous Floaters and Opacities” with talk “Matching the perspectives of the patient and the surgeon” FLORetina 2023, Rome Italy

2024

Program Co-Chairman, Panel Moderator 1) Cutting Edge Issues in Vitreoretinal Surgery, and 2) Retinal Diseases That Are Rare, Important, and Even Life Threatening, 52nd Aspen Retinal Detachment Society, Snowmass CO

Invited Faculty with lecture “Giant Retinal Tears: A Look Back and a Look Forward” at the VM Retina Meeting, Verona Italy (DD participation by recording and Q and A by live Zoom)

Panel Moderator for Wet AMD Symposium 1, and participant in Debate: Surgical Training After Fellowship, at the 42nd Annual Meeting of the American Society of Retina Specialists, Stockholm Sweden

Moderator for Session “Vitreoretinal Surgery 1” at Retina Subspecialty Day at the American Academy of Ophthalmology Annual Meeting, Chicago, IL

Open Medical Institute Ophthalmology Seminar with lectures “Advances and Controversies in the Management of Primary Retinal Detachment”, and “The Astonishing Development of Macular Surgery Over the Last Fifty Years”, Salzburg, Austria

Invited Faculty and Lead Moderator of Live Surgery; Co-Organizer of Symposium “Regional and Industry Perspectives on the Management of Vitreous Floaters and Opacities” with talk “Clinical Cases Illustrating How Their Management Has Changed In Recent Years”; Co-Moderator session “Retinal Detachment

with PVR” with talk “Obstacles to Improved Visual Results in Complex Retinal Detachment Surgery” FLORetina 2024, Florence, Italy

Invited Keynote lecture “Current Approaches to Primary and Complex Retinal Detachment for the General Ophthalmologist” (given in Italian) at the 79th meeting of the Società Oftalmologica Lombarda, Milan, Italy

2025

Co-Moderator Symposium “Ophthalmology Resident Clinics: Promises and Pitfalls” at the 2025 Annual meeting of the Association of University Professors of Ophthalmology (AUPO), Ft. Lauderdale FL

Program Co-Chairman, Panel Moderator 1) Let’s Talk Surgical Retina, and 2) Let’s Talk Retina, 53rd Aspen Retinal Detachment Society, Snowmass CO

Co- Moderator Symposium “International Surgical Retina” at the 2025 Annual Meeting of the Vit-Buckle Society, Austin TX

Invited speaker, the XXIV Infopoverty World Conference; How Could AI Fight Poverty Creating Well-being For All? with lecture “Synthetic Review of Current Telemedicine Projects in the World” United Nations Headquarters (live with webcast), New York NY