

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2024-00260

U.S. Patent No. 11,253,572

DECLARATION OF DR. CHRISTINE KAY

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TABLE OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 11,253,572
1003	Christine Kay <i>Curriculum Vitae</i>
1004	Institution Decision in <i>Apotex Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01524. (“Apotex ’572 ID”)
1005	Press Release, “Enrollment Completed in Regeneron and Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (September 14, 2009),” available at: https://newsroom.regeneron.com/news-releases/news-release-details/enrollment-completed-regeneron-and-bayer-healthcare-phase-3 (“2009 Press Release”)
1006	Press Release, “Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME),” Exhibit 99.1 to Regeneron 8-K filed on December 20, 2010, available at: https://yahoo.brand.edgar-online.com/displayfilinginfo.aspx?FilingID=7617341-6436-23571&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6 (“December 2010 Press Release”)
1007	Press Release, “Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration,” Exhibit 99.1 to Regeneron 8-K filed on November 22, 2010, available at: https://yahoo.brand.edgar-online.com/displayfilinginfo.aspx?FilingID=7572010-8611-26486&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6 (“November 2010 Press Release”)
1008	Apotex Petition for IPR filed in <i>Apotex Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01524 (Paper 1) (“Apotex Petition”)
1009	Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. <i>Expert Opin Investig Drugs</i> . 2009;18(10):1573-1580. (“Dixon”)
1010	Major JC et al., “DA VINCI: DME and VEGF Trap-Eye: INvestigation of Clinical Impact: Phase 2 Study in Patients With Diabetic Macular

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	Edema (DME), ARVO Annual Meeting Abstract (April 2010), Vol. 51, Issue 13, available at: https://iovs.arvojournals.org/article.aspx?articleid=2375028 (“2010 ARVO Abstract”)
1011	Final Written Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2021-00881 (Paper 94) (“338 FWD”)
1012	Institution Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01225 (Paper 21) (“681 ID”)
1013	Institution Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01226 (Paper 22) (“601 ID”)
1014	Certified Prosecution History of U.S. Patent No. 11,253,572 (“572 patent PH”)
1015	Adis R&D Profile, Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye. <i>Drugs R D</i> . 2008;9(4):261-269. (“Adis”)
1016	Hecht, “Ophthalmic Preparations,” Remington: The Science and Practice of Pharmacy, Volume II, 19th edition, Chapter 89 (1995). (“Hecht”)
1017	WO 2006/047325 A1 (“Shams”)
1018	Elman MJ, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. <i>Ophthalmology</i> . 2010 Jun;117(6):1064-1077.e35. (“Elman 2010”)
1019	Elman MJ, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. <i>Ophthalmology</i> . 2010 Jun;117(6):1064-1077.e35, published April 28 2010, available at https://www.aaojournal.org/article/S0161-6420(10)00243-5/fulltext (“Elman AAO Website”)
1020	Authenticating Affidavit and the July 13, 2010 Web Archive of the CATT Patient Eligibility Criteria, available at https://web.archive.org/web/20100713035617/http://www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf , attached as Exhibit B (“CATT Study”).

Exhibit	Description
1021	Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145(2):239-248. (“PIER Study”).
1022	Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (NCT00593450), available at: https://clinicaltrials.gov/ct2/show/NCT00593450 (“NCT-450”)
1023	Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145(2):239-248, published December 3, 2007, available at https://www.ajo.com/article/S0002-9394(07)00881-1/fulltext (“PIER AJO Website”)
1024	History of Changes for Study: A Study of rhuFab V2 (Ranibizumab) in Subjects With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD) (NCT00090623), available at: https://clinicaltrials.gov/ct2/history/NCT00090623?V_1=View#StudyPageTop . (“NCT-623”)
1025	ClinicalTrials.gov Background, available at: https://clinicaltrials.gov/ct2/about-site/background (“ClinicalTrials.gov Background”)
1026	ClinicalTrials.gov About the Results Database, available at: https://clinicaltrials.gov/ct2/about-site/results (“ClinicalTrials.gov About the Results Database”)
1027	Press Release, “Regeneron Reports Positive Phase 1 Data for the VEGF TRAP in Age-Related Macular Degeneration,” Exhibit 99(a) to Regeneron 8-K filed on May 2, 2006, available at: https://yahoo.brand.edgar-online.com/displayfilinginfo.aspx?FilingID=4380124-5423-15279&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6 (“May 2006 Press Release”)

Exhibit	Description
1028	Nguyen QD et al. A phase I study of intravitreal vascular endothelial growth factor trap-eye in patients with neovascular age-related macular degeneration. Ophthalmology. 2009 Nov;116(11):2141-8.e1. (“Nguyen 2009”)
1029	Press Release, “Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration” published on May 8, 2008, available at: https://investor.regeneron.com/node/10561/pdf (“May 2008 Press Release”)
1030	Do DV et al., “Results of a Phase I Study of Intravitreal VEGF Trap in Subjects With Diabetic Macular Edema: The CLEAR-IT DME Study,” ARVO Annual Meeting Abstract (May 2007), Vol. 48, Issue 3, available at: https://iovs.arvojournals.org/article.aspx?articleid=2384099 (“2007 ARVO Abstract”)
1031	Do DV et al., The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. Ophthalmology. 2011 Sep;118(9):1819-26 (published online on May 5, 2011). (“Do 2011”)
1032	Randolph and Jones, “Surfactant-Protein Interactions,” Rational Design of Stable Protein Formulations, edited by Carpenter and Manning, vol. 13, 2002 (“Randolph”)
1033	Fraser et al., Journal of Clinical Endocrinology and Metabolism, February 2005, 90(2):1114-1122 (“Fraser”)
1034	Lucentis ® Original Approved Labeling (2006), available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_Prntlbl.pdf (“Lucentis Label”)
1035	Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A. 2002;99(17):11393-11398. (“Holash”)
1036	Rudge JS, Thurston G, Davis S, et al. VEGF trap as a novel antiangiogenic treatment currently in clinical trials for cancer and eye diseases, and VelociGene- based discovery of the next generation of angiogenesis targets. Cold Spring Harb Symp Quant Biol. 2005;70:411-418 (“Rudge 2005”)

Exhibit	Description
1037	Gomez-Manzano C, Holash J, Fueyo J, et al. VEGF Trap induces antiglioma effect at different stages of disease. <i>Neuro Oncol.</i> 2008;10(6):940-945. (“Gomez-Manzano”)
1038	Heier JS, et al., Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. <i>Ophthalmology.</i> 2012;119(12):2537-2548. (“Heier 2012”)
1039	Heier JS, et al., CLEAR-IT 2 Investigators. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. <i>Ophthalmology.</i> 2011 Jun;118(6):1098-106. (“Heier 2011”)
1040	Pai A, El Shafei MM, Mohammed OA, Al Hashimi M., Current concepts in intravitreal drug therapy for diabetic retinopathy. <i>Saudi J Ophthalmol.</i> 2010 Oct;24(4):143-9. (“Pai 2010”)
1041	U.S. Patent App. Pub. US 2007/0190058A1 (“Shams US App. Pub.”)
1042	U.S. Patent No. 9,254,338 (“338 patent”)
1043	WO 2012/097019A1 (“Yancopoulos PCT Application”)
1044	U.S. Dep’t Health & Human Servs., Nat’l Inst. Health, Nat’l Eye Inst., “Diabetic Retinopathy: What You Should Know (Sept. 2015),” available at: https://www.nei.nih.gov/sites/default/files/healthpdfs/Diabetic_Retinopathy_What_You_Should_Know.pdf (“NIH DR”)
1045	U.S. Dep’t Health & Human Servs., Nat’l Inst. Health, Nat’l Eye Inst., “Age-Related Macular Degeneration: What You Should Know (Sept. 2015),” available at: https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf (“NIH AMD”)
1046	Halpern MT, Schmier JK, Covert D, Venkataraman K. Resource utilization and costs of age-related macular degeneration. <i>Health Care Financ Rev.</i> 2006;27(3):37-47. (“Halpern 2006”)
1047	Rudge JS, Holash J, Hylton D, et al. VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. <i>Proc Natl Acad Sci U S A.</i> 2007;104(47):18363-18370. (“Rudge 2007”)

Exhibit	Description
1048	Li E, Donati S, Lindsley KB, Krzystolik MG, Virgili G. Treatment regimens for administration of anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2020;5(5):CD012208. (“Li 2020”)
1049	Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology. 2009;116(1):57-65.e5. (“Brown 2009”)
1050	Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al, Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012; 119(7):1388-98 (“Martin”)
1051	Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al, Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012; 119(7):1399-411 (“Chakravarthy 2012”)
1052	Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006; 355(14):1419-31 (“Rosenfeld 2006”)
1053	Heimann, H. (2007). Chapter 5 Intravitreal Injections: Techniques and Sequelae. In: Holz, F.G., Spaide, R.F. (eds) Medical Retina. Essentials in Ophthalmology. Springer, Berlin, Heidelberg. (“Heimann 2007”)
1054	Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreal injection: a comprehensive review. Retina. 2004;24(5):676-698. (“Jager 2004”)
1055	Certified Prosecution History of U.S. Patent No. 10,130,681 B2 (“’681 patent PH”)
1056	Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (NCT00685854) (May 24, 2008), available at:

Exhibit	Description
	https://clinicaltrials.gov/ct2/history/NCT00685854?V_1=View#StudyPageTop (“MACTEL Study”)
1057	Authenticating Affidavit and the November 7, 2008 Web Archive of Ranibizumab Injections to Treat Macular Telangiectasia Without New Blood Vessel Growth (NCT00685854), available at https://web.archive.org/web/20081107014243/https://clinicaltrials.gov/ct2/show/NCT00685854 , attached as Exhibit A (“MACTEL Study Wayback Machine”)
1058	Using the Wayback Machine, available at: https://help.archive.org/help/using-the-wayback-machine/
1059	Eylea Label 2011, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf
1060	Glenn J. Jaffe, Paul Ashton, P. Andrew Pearson, Intraocular Drug Delivery (2006) (“Jaffe”)
1061	Steps for a Safe Intravitreal Injection Technique (2009), available at: https://www.retinalphysician.com/issues/2009/july-aug/steps-for-a-safe-intravitreal-injection-technique
1062	Mylan’s Emergency Motion to Modify Scheduling Order and For Emergency Status Conference filed in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , Case No. 1:22-cv-00061-TSK, Northern District of West Virginia. (Dkt. 415) (“Mylan April 10 Motion”)
1063	April 19, 2023 Claim Construction Order entered in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , Case No. 1:22-cv-00061-TSK, Northern District of West Virginia. (Dkt. 427) (“Mylan Litigation CC Order”)
1064	U.S. Patent No. 7,531,173 (“173 patent”)

I. INTRODUCTION

1. I have been retained by the law firm Gemini Law LLP on behalf of Celltrion, Inc., (hereinafter, “Petitioner”) to provide expert opinions concerning antagonists of Vascular Endothelial Growth Factor (“VEGF”) used as intravitreal injection for the treatment of angiogenic disorders such as age-related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion (CRVO), branch retinal vein occlusion, and corneal neovascularization.

2. Specifically, I have been asked to provide my opinions related to U.S. Patent No. 11,253,572 (“the ’572 patent”) (Ex. 1001) and the scientific and technical knowledge regarding the subject matter of the ’572 patent before and for a period following the earliest priority date of the application that led to the ’572 patent. For purposes of this expert declaration, I have been asked to assume that the earliest priority date of the ’572 patent is January 13, 2011 for all claims other than claim 25.

3. My opinions in this declaration are based on the documents I cite along with my professional training, experience and knowledge that I have acquired working in the field of ophthalmology during my career. I am being compensated for my services as an expert at my standard consulting rate of \$800/hr. My compensation is in no way contingent on the substance of my opinions or the outcome of this case.

4. My opinions and their underlying reasoning are explained in detail below.

II. BACKGROUND AND QUALIFICATIONS

5. I am an ophthalmologist with over 15 years of experience in the research, diagnosis, treatment, and analysis of vitreoretinal eye disorders. I received a B.A. degree in Neurobiology from Harvard University in 2001. I obtained my M.D. from the University of Florida (UF) in 2005. I completed an ophthalmology residency at the University of South Florida in 2009 where I was Chief Resident. I completed a Vitreoretinal Surgery Fellowship at the University of Iowa in 2011.

6. From 2009 to 2011, I was a clinical instructor for residents in both the clinic, surgery, and on-call. During this time, I also was a member of the Medical Student Lecture Series, where I lectured on Retinal Anatomy. I also served as a sub-investigator treating patients in the VIEW1 clinicals trials for exudative age-related macular degeneration during my fellowship.

7. From 2011 to 2014, I was an Assistant Professor at UF, where I taught residents and fellows in both the clinic and operating room, and gave lectures on retina and fluorescein angiography. During this time, I was on a Clinician-Scientist Tract funded by a Career Development Award by the Foundation Fighting Blindness, studying inherited retinal disease and gene therapy. I served as the Retina Fellowship co-Director. I additionally was a faculty instructor for a number of residency training courses, including an ophthalmology elective and a surgery clerkship. I mentored a number of graduate students in both retina fellowships and through dissertations

related to ophthalmology. During this time, I was also the Director of the Vitreoretinal Surgical Service and the Electrophysiology Service. From 2014 and continuing to the present day, I am an Affiliate Assistant Professor of ophthalmology at the University of South Florida, where I teach lectures to ophthalmology residents with an emphasis on inherited retinal disease.

8. I received numerous awards throughout my career. I have been involved in clinical or scientific research since college, winning the Harvard Hoopes Prize for Senior Thesis, awarded the Harvard College Research Program Grant and Harvard College Scholarship, as well as a Howard Hughes research grant for undergraduate research. In 2008, I was appointed the Chief Resident at University of South Florida's Ophthalmology Residency. In 2012, I received the Honor Award from the American Society of Retina Specialists (ASRS). In 2018, I received the ASRS Senior Honor Award which is awarded for participation in oral and poster presentations at the annual ASRS meetings. During my faculty appointment at UF I was awarded and partially funded by a Foundation Fighting Blindness, Career Development Award (2011 – 2016) which was a five-year award amount totaling \$375,000 for "Development and optimization of a viral gene delivery system for the treatment of CNGB3-associated Achromatopsia." I also served as co-PI partially funded by the NIH sponsored study grant on "Vascular Reparative Mechanism by ACE2/Ang-(1-7) in Diabetes" totaling \$914,139.

9. I was and/or currently am a member in several Professional and Academic Societies, including the Retina Society, the Macula Society, the American Society of Retina Specialists, the American Academy of Ophthalmology, ARVO, and the American Medical Association, among others. I am a member of WINR (Women in Retina), ASRS, and was a Steering committee member and Regional direct of RAFA (Retinal advocacy and federal affairs, committee of American Society of Retinal Specialists).

10. I have given over twenty poster presentations, over ten courses at national meetings, and at least thirty oral presentations at national meetings. I have authored or co-authored over forty publications, including peer-reviewed scientific papers and book chapters. The majority of these presentations and publications concerned retinal disease and other disorders of the eye.

11. I am currently Director of Clinical Research and Retinal Genetics Service at Vitreoretinal Associates and act as Principal Investigator on multiple (over 25 either ongoing or completed) clinical trials evaluating treatments either in inherited retinal disease, age related macular degeneration (both dry and wet), diabetic eye disease or retinal vein occlusion ("RVO"). My role in these trials has been that of principal investigator, either masked or unmasked treatment physician in intravitreal trials, and I am the vitreoretinal surgeon performing subretinal injections/vitrectomies in the gene therapy trials. I have also consulted for numerous pharmaceutical

companies in the area of retinal disease, including Atsena, Kodiak, Kiora, Ascidian, Astellas, Sanofi, and Novartis, among others.

12. My clinical practice is focused on the diagnosis and treatment of patients suffering from all diseases of the retina, including age-related macular degeneration, diabetic retinopathy, diabetic macular edema, and related disorders. I have experience with surgical interventions as well as the prescription and administration of various intravitreally-administered anti-angiogenesis agents. I routinely administer anti-VEGF agents as part of my practice, and have for over fifteen years.

13. In sum, I have over 15 years of hands-on clinical and research experience specializing in treating vitreoretinal disorders and the prescription, and intravitreal administration of VEGF antagonists. I have included a copy of my curriculum vitae in support of my opinions. Ex. 1003, Kay CV.

III. INFORMATION RELIED ON

14. In addition to my general knowledge gained as a result of my education and experience as an ophthalmologist, I have reviewed and considered, among other things, the '572 patent, the prosecution history of the '572 patent, and the prior art of record discussed herein.

15. I also considered the Final Written Decision ("FWD") issued by the Patent Trial and Appeal Board ("Board") in IPR2021-00881 ("the '338 IPR")

concerning U.S. Patent No. 9,254,338 (“’338 Patent”), finding all challenged claims there unpatentable. *See* Ex. 1011, ’338 FWD. I understand the ’338 and ’572 patents are in the same patent family and share the same specification. I have formed an opinion regarding the ’572 claims here independent of the ’338 FWD, but I found the ’338 FWD to be, in my judgment, consistent with my independent opinion expressed herein.

16. I further considered the Institution Decision in IPR2022-01226 (“’601 IPR”). I understand the ’601 IPR was instituted on January 11, 2023. Ex. 1013, ’601 ID. I have formed an opinion regarding the ’572 claims here independent of the ’601 ID, but I found the ’601 ID to be, in my judgment, consistent with my independent opinion expressed herein.

17. The full list of information, in addition to my professional, academic and clinical experience, that I have relied upon in forming my opinions for this report is set forth throughout the report and in the Table of Exhibits.

18. Where my conclusions are based on certain assumptions that I have adopted, I have stated such assumptions in this Declaration.

IV. RELEVANT LEGAL STANDARD

19. In forming my opinions and considering the patentability of the claims of the ’572 patent, I am relying upon certain legal principles that counsel for Petitioner have explained to me, as listed below.

20. I understand that for an invention claimed in a patent to be found patentable, it must be, among other things, new and not obvious in light of what came before it. Patents and publications which predated the invention are generally referred to as “prior art.”

21. For patent invalidity under an *inter partes* review, I understand the burden is on the party asserting unpatentability to prove it by a preponderance of the evidence. I understand that “a preponderance of the evidence” is evidence sufficient to show that a fact is more likely than not.

A. Person of Ordinary Skill in the Art

22. I have been informed that the claims of a patent are judged from the perspective of a hypothetical construct involving “a person of ordinary skill in the art” (“POSA”). The “art” is the field of technology to which the patent is related. I understand that the purpose of using a POSA’s viewpoint is objectivity. Thus, I understand that the question of validity is viewed from the perspective of a POSA, and not from the perspective of (a) the inventor, (b) a layperson, or (c) a person of extraordinary skill in the art. I have been informed that the claims of the ’572 patent are interpreted as a POSA would have understood them at the relevant time period (i.e., when the patent application was filed or the earliest effective filing date).

23. I have been informed that in the ’338 IPR, the petitioner proposed – and the Board adopted – the following definition for the relevant POSA:

A person of ordinary skill in the art at the time of the invention would have had (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

Ex. 1011, '338 FWD, 9-11.

24. I understand that in the '338 FWD, the Board found that petitioner's definition was "reasonable and consistent with the '338 Patent and the prior art or record." Ex. 1011, '338 FWD, 10.

25. Based on my review of the patent and prior art, I agree with the Board's definition of a POSA adopted in the '338 FWD, and in my opinion it should be adopted here consistent with the relevant art before the earliest priority of the '572 patent.

B. Claim Construction

26. I understand the first step in determining whether a patent claim is valid is to properly construe the claims. I understand that each claim of a patent subject to *inter partes* review is to be interpreted in light of the language of the claim, the written description, the figures, and the prosecution history of the patent.

27. I further understand that in the absence of a specific definition within the specification or the reliance on a specific meaning in the prosecution history, the terms as used in the challenged claims of the '572 patent are to be afforded their plain and ordinary meaning at the time of the invention.

28. I understand that the “plain and ordinary meaning” of a term means the ordinary and customary meaning given to the term by those of ordinary skill in the art at the time of the invention and that the ordinary and customary meaning of a term may be evidenced by a variety of sources, including the words of the claims, the specification, drawings, and prior art.

29. I understand that in construing claims all words in a claim must be considered in judging the patentability of that claim against the prior art.

30. I understand that extrinsic evidence may be consulted for the meaning of a claim term as long as it is not used to contradict claim meaning that is unambiguous in light of the intrinsic evidence. I also understand that in construing claim terms, the general meanings gleaned from reference sources must always be

compared against the use of the terms in context, and the intrinsic record must always be consulted to identify which of the different possible dictionary meanings is most consistent with the use of the words by the inventor.

C. Presumption of Validity

31. I understand that a granted patent is presumed to be valid. I understand that the presumption of validity can be overcome in district court litigations if clear and convincing evidence is presented that proves the patent is invalid. I understand that the standard of proof for invalidating a patent in an *inter partes* review proceeding is a “preponderance of the evidence” (i.e., greater than 50% chance of likelihood), which is a lower standard than the clear and convincing evidence standard.

D. Obviousness

32. I understand that even if a patent claim is not anticipated, it is still invalid if the differences between the claimed subject matter 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 of ordinary skill in the pertinent art.

33. I understand that a person of ordinary skill in the art provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

34. I also understand that an obviousness determination includes the consideration of various factors such as (1) the scope and content of the prior art, (2) the differences between the prior art and the asserted claims, (3) the level of ordinary skill in the pertinent art, and (4) the existence of secondary considerations or objective indicia of obviousness or non-obviousness.

35. I understand that an obviousness determination can be based on a single prior art reference or a combination of multiple prior art references or the knowledge of one of ordinary skill in the art. I understand that the prior art itself may provide a suggestion, motivation, or reason to combine or modify the teachings of the prior art, or that such a reason may come from other sources, such as the knowledge of a person having ordinary skill in the art, common sense, and market forces. I understand that the following rationales may support a finding of obviousness:

- combining prior art elements according to known methods to yield predictable results;
- simple substitution of one known element for another to obtain predictable results;
- use of known technique to improve similar devices (methods, or products) in the same way;
- applying a known technique to a known device (method or product) ready for improvement to yield predictable results;

- “obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
- some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

36. I understand that an obviousness determination requires a reasonable expectation of success in achieving the claimed invention.

37. I understand that the content of a patent or other printed publication (i.e., a reference) should be interpreted the way a person of ordinary skill in the art would have interpreted the reference as of the effective filing date of the patent application for the '572 patent. I have assumed that the person of ordinary skill in the art is a hypothetical person who is presumed to be aware of all of the relevant art at the time of the invention. The person of ordinary skill is not an automaton, and may be able to fit together the teachings of multiple patents employing ordinary creativity and the common sense that familiar items may have obvious uses in another context or beyond their primary purposes.

38. I understand that if an alleged invention is otherwise rendered obvious in view of the prior art, it is not patentable simply because the inventors discover an inherent property or a result that naturally flows from its application or use.

39. I understand that secondary considerations or objective indicia of obviousness or non-obviousness may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success or lack of commercial success of processes covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) the taking of licenses under the patent by others; (6) deliberate copying of the invention; (7) teaching away; and (8) the simultaneous invention of the claimed subject matter. I also understand that there must be a relationship between any such secondary considerations and the invention. I further understand that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

40. I understand that any secondary considerations or objective indicia must bear a nexus to the claimed invention. Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention. I further understand that the patentee bears the burden of demonstrating that the relevant commercial success is attributable to the claimed invention, as opposed to other

economic and commercial factors unrelated to the technical quality of the patented subject matter.

41. I understand that whether a prior art reference "teaches away" from the claimed invention is a fact to be considered in determining obviousness. I understand that it is improper to combine references where the references teach away from their combination. However, I understand that the nature of the teaching is highly relevant and must be weighed in substance - a known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use. Furthermore, I understand that the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.

42. I understand that hindsight must not be used when comparing the prior art to the invention for obviousness.

V. TECHNOLOGY BACKGROUND

A. Diabetic Retinopathy (DR)

43. DR "occurs when diabetes damages the tiny blood vessels in the retina, which is the light-sensitive tissue at the back of the eye." Ex. 1044, NIH DR, 1. DR "can cause blood vessels in the retina to leak fluid or hemorrhage (bleed), distorting vision." (*Id.*, 1-2). Further, "[i]n its most advanced stage, new abnormal blood

vessels proliferate (increase in number) on the surface of the retina which can lead to scarring and cell loss in the retina.” *Id.*, 2. DR is the “leading cause of vision impairment and blindness among working-age adults.” *Id.*, 1.

B. Diabetic Macular Edema

44. As noted above, in people with diabetes, too much blood sugar can damage the tiny blood vessels at the back inner wall of the eye (retina) or block them completely, causing diabetic retinopathy. With time, tiny bulges (microaneurysms) protrude from the vessel walls, leaking or oozing fluid and blood into the retina. This fluid can cause swelling (edema) in the central part of the retina (macula). This complication is called diabetic macular edema. Thus, DME is caused by DR. “DME is the most common cause of vision loss among people with diabetic retinopathy.” Ex. 1044, NIH DR, 3.

C. Age-Related Macular Degeneration (AMD)

45. Age-related macular degeneration (AMD) is a progressive degenerative disease of the macula, an area in the retina responsible for visual acuity and color vision. As its name implies, AMD increases in prevalence with age and is “a common eye condition and a leading cause of vision loss among people age 60 and older.” Ex. 1045, NIH AMD, 1. As of 2009, AMD “affect[ed] > 1.75 million individuals in the US and it [was] estimated that by 2020 this number will increase to almost 3 million.” Ex. 1009, Dixon, 1573.

46. There are three stages of AMD – early, intermediate, and late – which are determined by the size and number of miniscule lipid and protein bundles called drusen under the retina. Ex. 1045, NIH AMD, 7. Early AMD is diagnosed by several small or a few medium-sized drusen around the macula, but there are typically no symptoms or vision loss. *Id.* Individuals with intermediate AMD have larger drusen and/or pigment changes in the retina. *Id.* This may cause some vision loss but many individuals will not experience significant visual symptoms. *Id.*

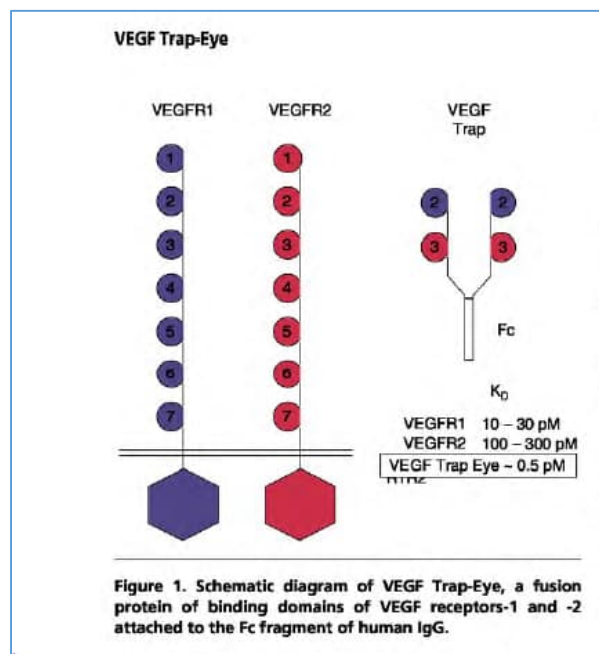
47. In addition to drusen, individuals with late AMD experience vision loss from damage to the macula. *Id.* Late AMD can be classified as either dry (*i.e.*, geographic atrophy) or wet (*i.e.*, neovascular AMD). *See, e.g.*, Ex. 1005, 2009 Press Release, 1; Ex. 1045, NIH AMD, 7-8. Dry AMD is the more common of the two, accounting for about 85 to 90 percent of AMD cases. *See, e.g.*, Ex. 1046, Halpern 2006, 37; Ex. 1009, Dixon, 1. It is estimated to be responsible for approximately 25% of patients with severe vision loss (defined as <20/200 visual acuity).

48. Wet AMD is less common but often more serious than dry AMD. The hallmark of wet AMD is the growth of irregular blood vessels under the retina. *See*, Ex. 1005, 2009 Press Release, 1-2; Ex. 1045, NIH AMD, 7-8. The leakage of fluid and blood from these vessels leads to exudation and hemorrhage. *Id.* Without treatment, the condition causes a permanent disciform scar beneath the retinal layers and results in central visual loss characteristic of the late-stage wet AMD. *Id.*

49. Laser and photodynamic therapy traditionally has been used as a treatment for wet AMD to prevent or delay the spread of leaky blood vessels by cauterizing them in the retinal layers. However, only a minority of patients are eligible to receive this treatment, and the treatment itself could cause acute retinal damage. Since their introduction in the early 2000s, intravitreal injections of VEGF antagonists have become the gold standard for treating angiogenic eye disorders, including AMD.

D. VEGF Trap-Eye/Aflibercept

50. VEGF Trap-Eye/Aflibercept is a fusion protein made up of Ig domain 2 of human VEGFR1 and Ig domain 3 of human VEGFR2 combined with a human IgG Fc fragment, as shown below:



Ex. 1009, Dixon, 1575-76, Fig.1. VEGF Trap-Eye/Aflibercept is developed by Regeneron and is a “fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PIGF).” Ex. 1005, 2009 Press Release, 1.

51. VEGF Trap/Aflibercept’s potential as a treatment for angiogenic disorders was reported in the literature well before 2011. For example, in 2002, Regeneron reported that VEGF-Trap/Aflibercept “has prolonged in vivo pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*” by binding to VEGF and reducing angiogenesis. Ex. 1035, Holash, 11393. Specifically in the context of eye disorders, Regeneron reported that “blocking VEGF-A has also been impressive in maintaining and improving vision in wet age related macular degeneration (AMD).” Ex. 1036, Rudge 2005, 411. Regeneron further disclosed that “[i]nitial clinical studies in human patients suffering from both AMD and diabetic edema and retinopathy appear quite promising, with evidence in early trials that the VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity.... The VEGF Trap is now entering more advanced clinical trials in vascular eye diseases.” *Id.*, 414-15.

52. Thus, POSAs understood before 2011 that VEGF Trap-Eye/Aflibercept showed efficacy in treating angiogenic diseases and was being studied as a promising treatment candidate for angiogenic eye disorders in particular.

53. In my opinion, it was also common knowledge among POSAs before 2011 that Regeneron's VEGF Trap was aflibercept, as I understood at the time.

54. For example, Dixon noted "[o]ne promising new drug is aflibercept (VEGF Trap-Eye)" for the treatment of AMD. Ex. 1009, Dixon, 1573. Dixon further taught that the two have "the same molecular structure." *Id.* at 1575. Further, numerous articles using the term aflibercept refer back to Holash and its description of VEGF TrapR1R2. *See, e.g.*, Ex. 1037, Gomez-Manzano, 940, 945 ("a new anti-VEGF agent, VEGF Trap/aflibercept (henceforth referred to as VEGF Trap), has been developed by incorporating domains of both VEGF receptor 1 (VEGFR1) and VEGFR-2 fused to the constant region of human immunoglobulin G1," and citing to Holash); Ex. 1015, Adis (treating "VEGF TRAP-Eye," "VEGF TRAP (R1R2)," and "aflibercept" as synonymous).

55. Moreover, Regeneron's prior art publications and patents confirm that the terms "VEGF Trap-Eye," "VEGF TrapR1R2," and "aflibercept" referred interchangeably to the same molecule having the same amino acid and nucleic acid sequences.

56. For example, Regeneron prior art patent disclosed that “[i]n a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trapR1R2) comprising the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQID NO: 2.” Ex. 1064, ’173 patent, 1:48-52. Regeneron used “aflibercept” as a keyword for its publication that described “VEGF Trap” and referred back to an earlier Regeneron publication disclosing the structure of “VEGF-TrapR1R2.” *See, e.g.*, Ex. 1047, Rudge 2007, 18363, 18370 (discussing “VEGF Trap” with “aflibercept” as a keyword, and describing “VEGF Trap” by citing back to Holash) that disclosed the structure of “VEGF-TrapR1R2”).

57. In view of these disclosures, a POSA would have understood the interchangeability of the terms “VEGF Trap-Eye,” “VEGF TrapR1R2,” and “aflibercept,” known aflibercept’s sequence information based on Regeneron’s prior art publications and patents, and recognized that it was being studied as possible treatments for angiogenic eye disorders.

E. Dosing Regimen for Intravitreal Injections of VEGF Antagonists

58. At the time of the alleged invention, practitioners in the industry focused on ways to minimize risks of complications from intravitreal injections such as infection, inflammation, and patient burden while maintaining efficacy of the anti-VEGF therapies in treating angiogenic eye disorders. The potential adverse effects

from injection had serious consequences for vision, including endophthalmitis, retinal hemorrhage, retinal detachment, RPE detachment, retinal edema, vitreous detachment, and total blindness. *See, e.g.*, Ex. 1009, Dixon, 1577; Ex. 1048, Li 2020, 9.

59. As a starting point, pivotal anti-VEGF trials followed monthly injection regimens to investigate drug efficacy. For example, initial trials of ranibizumab (Lucentis[®]), bevacizumab (Avastin[®]), and aflibercept (Eylea[®]) – the leading anti-VEGF candidates for treating eye disorders, the time – tested monthly administration of anti-VEGF agents for the treatment of AMD. *See* Ex. 1049, Brown 2009; Ex. 1050, Martin 2012; Ex. 1039, Heier 2011; Ex. 1051, Chakravarthy 2012; Ex. 1052, Rosenfeld 2006.

60. After a monthly dosing regimen showed effectiveness in treating AMD, subsequent trials investigated the efficacy of ranibizumab, bevacizumab, and aflibercept using a variety of less frequent, longer-interval dosing regimens to minimize complications and patient burden associated with monthly injections. For example, the VIEW trials disclosed in Dixon compared monthly injections of aflibercept with bimonthly injections after three initial monthly doses. Ex. 1009, Dixon, 1576. Results demonstrated comparable effects on BCVA due to aflibercept's longer therapy window than ranibizumab. Ex. 1039, Heier 2011; Ex. 1038, Heier 2012.

61. There is currently no standard regimen for injection frequency after the initial monthly loading doses. Although the labels for these VEGF-antagonists specify fixed dosing schedules, practitioners like myself administer anti-VEGF injections at frequencies that vary based on physician preference and individual patient response after the initial monthly loading doses. Ex. 1048, Li 2020. A POSA would have understood that the dosing regimens specified in the labels are a guide, not a requirement, and the actual injection schedule is routinely optimized based on patient need and compliance, treatment risks and effects, and overall cost effectiveness.

F. Exclusion Criteria Intended to Reduce Risks Associated with Intravitreal Injections

62. As discussed above, it was understood by POSAs well before 2011 that intravitreal administration could result in serious complications such as infections and inflammations. *See, e.g.*, Ex. 1009, Dixon, 1577 (“Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.”); Ex. 1053, Heimann 2007, 67 (noting that “although severe ocular adverse events associated with intraocular injections are rare, the rate can increase significantly if certain standards for intraocular interventions are not followed”); *see also* Ex. 1038, Heier 2012, 2537 (noting “[t]he risk of rare but serious adverse events resulting from the intravitreal procedure, together with the

significant burden of making monthly visits to their retinal specialist, have led to extensive efforts to decrease injection and monitoring frequency.”).

63. For example, a POSA would have understood that conjunctivitis, keratitis, scleritis, and endophthalmitis were ocular and/or periocular types of infections or inflammations, usually caused by bacteria, viruses, or fungi. Ex. 1053, Heimann 2007, 67 (“Endophthalmitis ... is usually caused by bacterial contamination during or immediately after the injection”); *id.*, 77 (“The spectrum of cultured organism shows a greater variation of different bacterial species causing endophthalmitis.”).

64. Endophthalmitis in particular was considered “the most feared complication of intravitreal injections” that “can progress extremely quickly without appropriate treatment with potentially devastating consequences.” Ex. 1053, Heimann 2007, 67, 76; Ex. 1054, Jager 2004, 678 (“[E]ndophthalmitis ... generally ha[s] the greatest likelihood for acute and irreversible vision loss.”).

65. The risk of inflammation and infections associated with frequent intravitreal injections was a well-known problem in the art, as applicants during prosecution of the ’681 patent, a related patent to the ’572 patent in the same patent family, also acknowledged: “[Monthly] treatment protocol is (1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the

patient to potential adverse effects such as infection with each treatment event.” Ex. 1055, ’681 PH, 489.

66. Thus, POSAs recognized that exclusion criteria are designed to minimize complications associated with intravitreal injections and understood the importance of performing a thorough pre-operative assessment of the patient before proceeding to the injection in order to avoid known complications associated with the intravitreal injection procedure. See Ex. 1053, Heimann, 81 (recommending that a “thorough preoperative assessment including funduscopy should be performed before any intravitreal injection to confirm the need for the injection and to rule out possible contraindications or to detect conditions that might complicate the injection[.]”). Conditions such as infections and inflammations would therefore generally contraindicate the use of an intravitreally administered agent.

67. POSAs also understood that recent ocular or periocular infection (*e.g.*, within the 2 weeks prior to screening) could negatively influence the outcome and reliability of a clinical trial. For instance, such recent ocular or periocular infection can (1) increase the risk of serious complications such as endophthalmitis that may jeopardize a patient’s vision and/or cause the patient to have to drop out of the study; (2) skew the baseline and/or post-administration measures of visual acuity, retinal thickness, and/or other anatomic assessments; and (3) impact the pharmacokinetics of administered drugs after intravitreal injection. Ex. 1054, Jager 2004, 680.

68. Infections and inflammations in particular can mimic some of the anatomical characteristics of AMD, including swelling and the presence of fluid, and may obscure proper diagnosis of the underlying disease. See Ex. 1053, Heimann 2007, 75 (noting that intravitreal injections can cause “severe intraocular inflammatory reactions” and acknowledging that it can be “extremely difficult, to differentiate a sterile inflammatory process from an inflammatory reaction associated with infectious endophthalmitis”); Ex. 1054, Jager 2004, 679-680 (noting “[p]harmacokinetic characteristics are dependent on both the anatomical and physiologic features at the site of administration...[and] [t]he pharmacokinetic properties of compounds in the vitreous have been observed to change in the setting of inflammation or infection”).

69. POSAs were also aware of the exclusion criteria commonly used in clinical studies of other leading anti-VEGF agents for the treatment of vitreoretinal disorders. Such exclusion criteria include those disclosed in the CATT Study, MACTEL Study, and PIER Study involving bevacizumab (Avastin) and ranibizumab (Lucentis). See Sections X.A.8 and X.B.8 below.

VI. BACKGROUND OF THE '572 PATENT

A. General Description

70. I understand that the '572 patent is entitled “Using a VEGF Antagonist to Treat Angiogenic Eye Disorders.” The '572 patent issued on February 22, 2022.

I understand that it will expire on January 11, 2032. The '572 patent names as its sole inventor, George Yancopoulos.

71. I understand that the '572 patent specification discloses that “the methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist” to treat angiogenic eye disorders, *i.e.*, eye disorders caused by or associated with the formation of new blood vessels. Ex. 1001, Abstract, 1:40-2-57. According to the specification, the formation of new blood vessels requires, among other things, the differentiation of endothelial cells that are dependent on Vascular Endothelial Growth Factor (VEGF). *Id.*

72. In particular, the methods “comprise sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonists.” *Id.* at 2:12-41.

73. I understand that Examples 1-6 of the '572 patent describe certain results of Phase I, II or III clinical trials using different dosing regimens of “VEGF Receptor-Based Chimeric Molecule (VEGFT)” in subjects with neovascular AMD (Examples 1-4), DME (Example 5), or macular edema secondary to CRVO (Example 6). *See generally id.* at Cols. 8-18. I note that Example 7 of the '572 patent describes additional dosing regimens, but does not contain any test results. *Id.*

B. Prosecution History

74. I understand that the '572 patent issued from U.S. Application No. 17/352,892 ("892 application"), filed on June 21, 2021. Ex. 1014, '572 patent PH. I reviewed the prosecution history of the '892 application.

75. I understand that on October 28, 2021, the Examiner issued a non-final office action rejecting the pending claims on the ground of non-statutory obviousness-type double patenting as being unpatentable over certain claims of U.S. Patent Nos. 9,254,338 ("338 patent"), 9,669,069 ("069 patent"), 10,130,681 ("681 patent"), 10,828,345 ("345 patent") and 10,888,601 ("601 patent"). *Id.*, 1239-1245. I understand that the Examiner stated that while claims of these patents recite different dosing schedules, "it is routine experimentation to optimize dosages and dosing schedules." *Id.*

76. I understand that the applicants submitted terminal disclaimers to the reference patents, which limited the expiration date of the '572 patent to that of the reference patents listed above. *Id.*, 1315-1319. I understand that the applicants did not argue that the dosing regimens or visual acuity results were unexpected or otherwise rendered the claims patentable. *Id.*

77. I understand that on December 22, 2021, the Examiner issued a notice of allowance for the claims. *Id.*, 1334-1340.

VII. CHALLENGED CLAIMS

78. I understand that independent claims 1, 15, 26, and 29 are directed to methods for treating an angiogenic eye disorder or age-related macular degeneration by administering a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses 4 weeks apart, and one or more tertiary doses 8 weeks apart. I further note that the independent claims recite methods for treating “a patient in need thereof,” not an entire patient population or a percentage. I understand that these claims do not recite efficacy for a broader population or recite that the regimen be more efficacious than other regimens.

79. I understand that the four independent claims differ in their recitation of “results limitations” and indications. Claim 15 is directed to DME and does not recite any visual acuity results. Claim 1 is directed to any angiogenic eye disorder and recites a gain in visual acuity within 52 weeks after the initial dose. Claims 26 and 29 are directed to AMD and recite that the method be as effective as monthly administration of 0.5 mg of ranibizumab by intravitreal injection at 52 weeks following the initial dose. Dependent claims 2-5, 8-11, 16-17, 20-21, 24, and 27-28 and 30 further specify the number of secondary doses, gains in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score, and weeks to achieve the efficacy results. Dependent claims 6-7, 12-13, 18-19 and 22-23 recite that the aflibercept is formulated as an isotonic solution

or with a nonionic surfactant. Dependent claim 14 recites two exclusion criteria. Claim 25 recites that the number of initial loading doses for treating DME is five total.

VIII. CLAIM CONSTRUCTION

80. Given the similarities between the claims in the '572, '338, '601, and '681 patents and based on my review of the '338 FWD, '601 ID, and '681 ID, I agree with the constructions adopted by the Board in the '338 IPR, '601 IPR, and '681 IPR, and that the same constructions should apply here. Below I walk through the Board's reasoning, which is consistent with my understanding of how the terms would be understood by a POSA based on its knowledge of the art and the intrinsic evidence.

A. "A method for treating..."

81. I have analyzed the '572 patent specification and claims and have not seen any particular evidence set forth in the Challenged Claims or any guidance from the specification that would require some specialized meaning for the "method for treating" preamble and claim term. Consequently, in my opinion, a POSA would apply a plain and customary meaning to this term, which would include administering a therapeutic agent to a patient with a purpose of treating a patient but would not require any particular level of efficacy.

82. In the '338 FWD, evaluating the same specification and a similar preamble (“a method of treating an angiogenic eye disorder in a patient”), the Board found “that the intrinsic evidence supports finding that it is the administration of the VEGF antagonist to [a] patient for the purpose of providing an improvement of or beneficial effect on their angiogenic eye disorder that satisfies the “treating” portion of the preamble.” *Id.* at 19; *id.* at 23. I agree with that understanding, and the same reasoning applies to the preamble here. In other words, administration of aflibercept to a patient for the purpose of treating them using the recited dosing regimen is sufficient to meet the preamble’s “treating.”

83. This is consistent with the specification. The specification discusses the “Amount of VEGF Antagonist Administered” (*see* Ex. 1001, 6:49–7:53) as follows: “The amount of VEGF antagonist administered to the patient in each dose is, in most cases, a therapeutically effective amount.” *Id.* The specification further states that “the phrase ‘therapeutically effective amount’ means a dose of VEGF antagonist that results in a detectable improvement in one or more symptoms or indicia of an angiogenic eye disorder, or a dose of VEGF antagonist that inhibits, prevents, lessens or delays the progression of an angiogenic eye disorder.” *Id.* at 6:48-55 (emphasis added). In other words, the specification confirms that “therapeutically effective amounts” can range from an improvement to merely

inhibiting, preventing, lessening, or delaying progression—there is no particular level of efficacy required.

84. Moreover, this is also consistent with the Challenged Claims. For example, claim 30 specifies that “maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA)” and claim 17 specifies that “the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA).” Given that both of these outcomes—a loss of less than 15 letters and a gain of at least 9 letters—are within the claimed range for “treating,” a POSA would have understood that no particular level of efficacy is required.

85. Thus, in my opinion, consistent with the claim language and specification, the “method of treating” limitations require only that the recited method be administered, and that it has the purpose of treating a patient to achieve an improvement or beneficial effect—not that it achieves a particular level of efficacy.

B. “Exclusion Criteria”

86. I understand that in the ’601 ID, the Board found that the exclusion criteria recited in the non-DR/DME claims of the ’601 patent, which are the same criteria recited in claim 14 of the ’572 patent, are entitled to no patentable weight, and thus should not be treated as claim limitations. Ex. 1013, ’601 ID, 12-15; *see also* Ex. 1012, ’681 ID, 18-20. I understand that the Board found that “there is little

question that the exclusion criteria are directed to informational content.” I further understand that the Board found that the exclusion criteria lacked a functional relationship to the rest of the claims, particularly because “the claims do not expressly recite any positive step to be performed (or negative step not to be performed) should a patient meet the exclusion criteria.” Ex. 1013, ’601 ID, 14; *see also* Ex. 1012, ’681 ID, 19.

87. Moreover, I understand that the district court in *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, NDWV-1-22-cv-00061 (“Mylan Litigation”) similarly found that the exclusion criteria are not entitled to patentable weight. Ex. 1063, Mylan Litigation CC Order, 29-37. I understand that the court specifically found that “since there is no **requirement** to take new action that flows from the ‘wherein the exclusion criteria for a patient include...’ information, in a way that changes the existing treatment method, this claim language is construed to have no patentable weight.” *Id.*, 37 (emphasis original).

88. For purposes of this declaration, I have been asked to assume that the exclusion criteria recited in claim 14 of the ’572 patent are not entitled to patentable weight, unless noted otherwise below.

89. Additionally, below I list what I consider to be the plain and ordinary meaning of the conditions recited in the exclusion criteria:

Recited Condition	Plain and Ordinary Meaning
Active intraocular inflammation	Active, on-going inflammation in the interior of the eye, including the uvea
Active ocular or periocular infection	Active, on-going infection in or on the eye (including the anterior and posterior Sections) (“ocular”) or in the area surrounding the eye and within its orbit (i.e. the conjunctiva or muscles controlling the eye, etc.) (“periocular”)

90. As I discuss below, it would have also been obvious to exclude patients both from receiving intravitreal injections in infected/inflamed eyes in view of a POSA’s common knowledge and the explicit disclosures in the art.

IX. PRIORITY DATE

A. Applicable Legal Standard

91. I understand that in order for a patent to claim an effective priority date of an earlier application, that earlier application must provide a written description of the claims of the invention. I understand that this means Patent Owner must show that the specification reasonably conveys to a POSA possession of the claimed invention. I also understand that if the Challenged Claims lack written description support of its specification, then the Challenged Claims are only entitled to an effective filing date of the application that provides written description support.

92. I understand written description demands that the specification describe the invention in clear, concise, and exact terms as to allow a person skilled in the art to make and use the invention. It is my understanding that this involves two separate

requirements, the written description requirement and the enablement requirement. For written description, the patent must describe the invention such that a person of ordinary skill in the art would believe that the inventors had possession of the claimed invention at the time of the application. As to the enablement requirement, the patent must describe how to make and use the invention so as to enable a person of ordinary skill in the art to make and use the full scope of the invention without undue experimentation.

93. I understand that the enablement requirement is met only when a person of ordinary skill in the art, after reading the specification, could practice the asserted invention without undue experimentation. I understand that the full scope of the asserted invention must be enabled. I understand that I should consider several factors in determining whether the level of disclosure in the patent would require undue experimentation and show a lack of enablement, including: (1) the quantity of experimentation; (2) the amount of direction or guidance present; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

94. More particularly, I understand that laundry list disclosures are insufficient to satisfy the written description requirement when there is no further

guidance (“blazemarks”) provided about which species or combination of species included as part of the list may be selected to arrive at the claimed invention.

B. Claim 25 of the '572 Patent Has an Earliest Effective Filing Date of July 12, 2013 at Best

95. For purposes of this declaration, I have been asked to assume that the earliest priority date of the '572 patent is January 13, 2011 for all claims other than claim 25. As discussed below, it is my opinion that claim 25 of the '572 patent has an earliest effective filing date of July 12, 2013 at best.

96. I understand that claim 25 depends from 15 and requires the treatment of diabetic macular edema through administering a single initial dose of 2 mg of aflibercept, followed by “four secondary doses” 4 weeks apart, followed by tertiary doses 8 weeks apart. I understand that such a dosing regimen was not described in the specification of any application to which the '572 patent claims priority until July 12, 2013.

97. I understand that on July 12, 2013, Application 13/940,370 (the “'370 application”) was filed, which issued as the '338 patent, adding Example 7’s general listing of various dosing regimens in the specification. Ex. 1042, '338 patent.

98. Prior to that addition, the only disclosure of the use of five initial loading doses that I see was in a paragraph stating that “[t]he methods of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of a VEGF antagonist.” Ex. 1043, Yancopoulos PCT Application,

[0019]. That paragraph further states “[f]or example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.* 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient.” *Id*; *see also*, Ex. 1001 at Col. 4:22-31.

99. I also note that (unlike the prior art discussed below) there is no mention of the recited interval between secondary doses in this paragraph (4 weeks), no mention of the recited dosage amount in this paragraph (2.0 mg), no mention of the recited indications (DME), nor any indication of a specific combination of those variables would be for the treatment of DME as claimed. *See* Ex. 1043. Nor is there any indication in this paragraph that the tertiary doses associated such a regimen could be extended to 8 weeks. *Id*. Finally, there is no specific guidance in this paragraph or anywhere else in the specification to the use of 5 initial loading doses in the specific combination of dosing amount and secondary and tertiary intervals for the treatment of DR or DME. *Id*.

100. In fact, the specification mentions at least eight different numbers of initial doses (one to eight, “etc.”), five intervals for the secondary doses and 14 (“or more”) intervals for the tertiary doses, as well as 17 different disorders. *See* Ex. 1043; *see also* Ex. 1001, Cols. 3-7. And, because the specification recites “etc.” and “or more” for these variables, the possibilities are effectively infinite.

101. In view of this, it is my opinion that prior to July 12, 2013, a POSA would not have been able to arrive at the recited combination in claim 25 out of these near infinite number of combinations.

102. In my opinion, a POSA would have had no reason to conclude that the applicants were in possession of the claimed invention, at least prior to the July 12, 2013 date, because there is no specific guidance to the claimed invention. A POSA would have to select the recited combination of two different dosing intervals, a dosing amount, and an indication for treatment themselves.

103. On this basis, I understand that the pre-July 12, 2013 specifications lack adequate written description and thus Patent Owner cannot claim earlier priority to any earlier application.

X. INVALIDITY UNDER 35 U.S.C. § 103

A. Overview of the Prior Art

1. September 14, 2009 Press Release

104. I understand Regeneron's September 14, 2009 Press Release ("2009 Press Release"), titled "Enrollment Completed in Regeneron and Bayer HealthCare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)," was published on September 14, 2009. Ex. 1005. I was familiar with the clinical studies of aflibercept that it describes for AMD and DME at the time. I understand that the September 14, 2009 Press Release was cited during prosecution, but never substantively addressed by the Examiner.

105. The September 14, 2009 Press Release discusses VEGF Trap-Eye, also known as aflibercept. *See, e.g.*, Ex. 1015, Adis; Ex. 1009, Dixon. It discusses a number of clinical trials for various indications of VEGF Trap-Eye, including AMD and DME. As to DME, the press release specifically states that VEGF Trap-Eye is “in Phase 2 development for the treatment of Diabetic Macular Edema (DME).” Ex. 1005, 1. It teaches that the trial will involve a number of different dosing regimens, including an arm consisting of 2mg of VEGF Trap-Eye administered via three monthly loading doses followed by dosing every eight weeks: “VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses.” *Id.*

2. November 22, 2010 Press Release

106. I understand that Regeneron’s November 22, 2010 Press Release (“November 2010 Press Release”), titled “Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration,” was published on November 22, 2010. Ex. 1007. I was familiar with the clinical studies of aflibercept for AMD that it describes at the time. I understand that the November 2010 Press Release was cited during prosecution, but never substantively addressed by the Examiner.

107. I understand that the November 2010 Press Release discloses the top-line results of the VIEW 1 and VIEW 2 studies for the treatment of wet AMD with aflibercept. Ex. 1007. In addition to describing the treatment dosing arms tested in the VIEW 1 and 2 studies, it includes a summary of the efficacy data. I understand that the November 2010 Press Release discloses mean improvements in vision of between 7.9 and 8.9 letters at 52 weeks versus baseline in the dosing arm with bimonthly doses following three initial monthly doses. *Id.*, 4

3. December 20, 2010 Press Release

108. I understand that the December 20, 2010 Press Release (“December 2010 Press Release”), titled “Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME),” was published on December 20, 2010. Ex. 1006. I understand the December 2010 Press Release was cited during prosecution but was never substantively addressed by the Examiner. I was familiar with the clinical studies of aflibercept for DME and CRVO that it describes at the time.

109. I understand that the December 2010 Press Release discloses the study design and results of the Phase II DA VINCI study for the treatment of DME with aflibercept. Ex. 1006. It discloses that the DA VINCI study included a study arm with three initial monthly doses of 2mg aflibercept followed through week 52 by

either every two months dosing or PRN (as-needed) dosing. *Id.*, 1-2. It further includes efficacy data showing mean changes in visual acuity of 8.5 and 9.7 letters at weeks 24 and 52 respectively in the dosing arm with bimonthly doses following three initial monthly doses. *Id.*, 2-3.

4. Dixon

110. Dixon et al., “VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration,” *Expert Opin. Investig. Drugs*, 18(10): 1573-80 (2009)) (“Dixon”) is a peer reviewed publication describing the various aflibercept clinical trials, including the Regeneron Phase Phase III clinical trials known as VIEW 1 and VIEW 2. Ex. 1009. Dixon was published in 2009.

111. I understand that Dixon describes the clinical trial results associated with administering aflibercept to treat neovascular AMD. *Id.* 1573. Dixon discloses that “VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD.” *Id.* Dixon discloses that in a Phase II trial, AMD patients who received four initial monthly doses, followed by only an average of 1.6 additional injections through 52 weeks (for a total of ~5.6 doses in a year on average), achieved a mean of 9 letter gains, with 29% gaining greater than 15 letters, by 52 weeks. *Id.*, 1576.

112. As discussed above, Dixon further describes VEGF Trap-Eye as “a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a

human IgG Fc fragment.” Ex. 1009, 1575. Dixon also discloses that “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure, but there are substantial differences between the preparation of the purified drug product and their formulations.” *Id.*

113. Dixon discloses that a Phase III trial of aflibercept “will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks.” Ex. 1009, 1576.

5. Hecht

114. Hecht is a chapter in *Remington: The Science and Practice of Pharmacy*, Volume II, published in 1995. I understand that Hecht was never substantively considered by the Examiner during prosecution.

115. Hecht provides guidance on formulating ophthalmic solutions for injection and teaches that ophthalmic solutions “are formulated to be sterile, isotonic and buffered for stability and comfort.” Ex. 1016, Hecht, 1569. Hecht further states that “[g]iven a choice, isotonicity always is desirable and particularly is important in intraocular solutions.” *Id.* at 1571. Moreover, Hecht teaches that nonionic surfactants should be used in ophthalmic solutions because they are “least toxic to

the ophthalmic tissues,” and they can act “as aids in achieving solution clarity,” or “as cosolvents to increase solubility.” *Id.*

6. Shams 2006

116. Shams is a Genentech patent application, titled “Method for treating intraocular neovascular diseases, and generally relates to methods for treating an intraocular neovascular disorder with a VEGF antagonist. Ex. 1017. Shams published in 2006. *Id.*

117. Shams disclosed monthly dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist. Ex. 1017, Shams. Shams explained that “a treatment schedule comprising an initial interval of administration of a therapeutic compound [an VEGF antagonist], followed by a subsequent, less frequent interval of administration of the therapeutic compound” allows “one to decrease subsequent doses of the therapeutic compound, while at the same time maintaining the therapeutic efficacy.” *Id.*, 21; *see also id.*, 4-5.

118. Shams further explains that “[t]he specific time schedule [for administering doses] can be readily determined by a physician having ordinary skill in administering the therapeutic compound by routine adjustments of the dosing schedule within the method of the present invention [i.e. loading and maintenance dosing]. *Id.*, 22-23. The time of administration of the number of first individual and

second individual doses as well as subsequent dosages is adjusted to minimize adverse effects while maintaining a maximum therapeutic effect.” *Id.*

7. Elman 2010

119. Michael J. Elman, MD, et al., Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema, *Ophthalmology* (June 2010) (“Elman 2010”) published in 2010 and describes a Phase 3 ranibizumab for the treatment of DR/DME.

120. At the time of Elman 2010, the VEGF antagonist ranibizumab (Lucentis®) was only approved for treatment of wet AMD, and other than short term studies, it had not been studied, particularly longer term or against the standard of care, for DME. Ex. 1018, 1076. Among its study arms, the Elman 2010 study tested a 52-week treatment protocol for ranibizumab under which an initial injection of ranibizumab (at “week 0”) was followed by injections at the 4, 8, and 12 week visits, for a total of 4 initial injections. *Id.* Patients in this arm received either “prompt laser” treatment during the initial dosing period (a standard treatment at the time that used a photocoagulation as part of treatment to remove abnormalities on the retina) or “deferred laser”—use of a photocoagulation laser only at or after 24 weeks if called for by the study protocol. The deferred laser group, in particular, is relevant here as the most direct evidence of the effect of an anti-VEGF agent on DR/DME without further complicating variables.

121. After the required fourth initial monthly dose was given according to the Elman 2010 protocol, clinicians thereafter performed an assessment every month (through week 52) in conjunction with a real-time data entry system referred to as a “Retreatment Algorithm,” and categorized patients as “success,” “improvement,” “no improvement,” or “failure.” Ex. 1018, Elman 2010, 1066, 1077, Appendix 2. The designation “depend[ed] mostly on visual acuity and OCT [“optical coherence tomography”] measurements.” *Id.* Optical coherence tomography (OCT) is a noninvasive, high-resolution imaging technique to measure retinal thickness, among other measures. Based on that assessment, clinicians were guided as to whether to provide another injection that month or not.

122. According to the Retreatment Algorithm, at the fifth and sixth visits, an injection of ranibizumab was required for patients in the ranibizumab + deferred laser group that were determined to meet the “no improvement” or “failure” criteria. If the “success” criteria was met, an injection was at investigator discretion. Ex. 1018, Elman 2010, 1077. In the deferred laser group, this approach resulted in an injection at least 78% of patients receiving a fifth initial monthly doses (i.e. an injection at the fifth visit). *Id.* at 1067 (reporting that 22% of patients did not receive a fifth dose).

123. Elman 2010 does not specifically report how many patients received an injection at the sixth visit. It does report that for the deferred laser group, however,

that the “median number of study drug injections before the 1-year primary outcome visit was... 9 (6, 11) ranibizumab injections (of 13 maximally possible injections).” Ex. 1018, 1067. This means that Elman 2010 teaches both that at least 78% of patients received a fifth dose and, if the median is applied to those 78% of patients, they received only four additional doses out of the eight possible doses remaining after their fifth injection.

124. While Elman does not provide sufficient data to determine exactly the median number of additional doses for the 78% of patients specifically (as opposed to the full group of deferred laser patients), the data would suggest to a POSA that DR/DME could be treated by an initial set of at least five monthly doses and then—as shown in other studies of anti-VEGF agents—could be followed by more widely-spaced maintenance dosing.

125. The use of longer intervals for treatment after the initial monthly loading doses is further supported by the discussion in Elman 2010, which states that there is a need to “follow eyes continuously undergoing this treatment because the results indicate that additional ranibizumab or focal/grid laser, or both, are needed in most eyes through at least 2 years, even if ‘success’ criteria are met early in the course of treatment.” Ex. 1018 at 1074.

126. In the discussion Section, Elman 2010 concludes that “[t]he observed benefits of intravitreal anti-VEGF treatment for DME in this study are consistent

with shorter-term improvements in visual acuity outcomes and resolution of DME on OCT noted with bevacizumab and ranibizumab.” Ex. 1018 at 1076. It further notes that the study results support the use of anti-VEGF agents generally, and by themselves, for DME, consistent with past findings: “Results from these and other studies should complement knowledge regarding the safety and efficacy of ranibizumab and other anti-VEGF drugs, alone, or in combination with laser, for the treatment of DME.” *Id.*

8. CATT and PIER Studies

127. As noted above, by 2010, POSAs were aware of multiple prior art publications that describe the relevant exclusion criteria, including publications documenting the CATT study, a Lucentis-Avastin trial comparing Avastin[®] (bevacizumab) and Lucentis[®] (ranibizumab) (“CATT Study” (Ex. 1020)), the MACTEL Phase 2 trial (a pilot study for Lucentis (ranibizumab)) (“MACTEL Study” and “MACTEL Study Wayback Machine” (Ex. 1056-57)), and the PIER Study evaluating the efficacy and safety of ranibizumab (“PIER Study” (Ex. 1021)).

128. These publications teach the use of exclusion criteria in relation to the two leading anti-VEGF agents (*i.e.*, Avastin[®] (bevacizumab) and Lucentis[®] (ranibizumab)) used to treat angiogenic eye diseases at the time, both of which were administered via intravitreal injections. In my opinion, a POSA would have understood that these publications identify active and recent inflammation or

infection in the eye as exclusion criteria for patients receiving treatment. The table below reproduces the recited exclusion criteria on the left, with the relevant corresponding exclusion criteria from the prior art CATT and PIER studies on the right:

Table 1	
Exclusion Criteria Recited in Claims 17, 25, and 33	Prior Art Exclusion Criteria for Anti-VEGF Intravitreal Injections Relied on by Petitioner
“(1) active intraocular inflammation ” – i.e. current inflammation within the eye	“Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye.” Ex. 1020, CATT Study, 6-7. “Active intraocular inflammation (grade trace or above) in the study eye.” Ex. 1021, PIER Study, 248.e3.
“(2) active ocular or periocular infection ” – i.e. a current infection anywhere on/in the eye (ocular) or surrounding it within its orbit (periocular)	“Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.” Ex. 1020, 6-7. “Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.” Ex. 1021, 248.e3.

a) The CATT Study Exclusion Criteria

129. The CATT Study evaluated the efficacy and safety of intravitreal injections of Avastin® (bevacizumab) relative to Lucentis® (ranibizumab), the two major anti-VEGF treatments for angiogenic diseases, both of which were administered intravitreally. See Ex. 1022, NCT00593450, ClinicalTrials.gov

(available at <https://clinicaltrials.gov/ct2/show/NCT00593450>). I understand that the University of Pennsylvania was the sponsor of the study. *Id.*

130. I understand that Exhibit 1020 includes an affidavit by the Internet Archive that confirms that the CATT Study publication was captured on July 13, 2010 by the Wayback Machine – a digital archive of the World Wide Web operated by the Internet Archive with which I am familiar. Ex. 1020, CATT Study; *see also* Ex. 1058, Using the Wayback Machine. I understand that Exhibit 1020 shows that the CATT Study, including details such as its exclusion criteria, was available and known to POSAs at the latest by July 13, 2010. *Id.* I was also familiar with the CATT Study during the time it was conducted.

131. The CATT Study exclusion criteria expressly list both active inflammation and active infections (the first two exclusion criteria listed in claims 1 and 14), as well as “recent (within 4 weeks) intraocular inflammation”:

EXCLUSION CRITERIA
Subjects who meet any of the following criteria will be excluded from study entry:

Exclusionary Concurrent Ocular Conditions
• Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period. • Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye • Current vitreous hemorrhage in the study eye • History of rhegmatogenous retinal detachment or macular hole in the study eye • History of vitrectomy in the study eye • Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye • Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia

Ex. 1020, CATT Study, 2.

b) The PIER Study

132. The PIER study evaluated the efficacy and safety of ranibizumab (Lucentis) administered monthly for three months and then quarterly in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Ex. 1021, PIER Study. Regillo et al., “Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1,” *Am. J. Ophthalmol.*, 145(2): 239-248 (Feb. 2008), published February 2008, describes the PIER Study. *Id.* I was familiar with the PIER Study during the time it was conducted. The PIER Study, including details such as its exclusion criteria, would have been available to POSAs at the time.

133. The PIER Study discloses the following exclusion criteria that include “any intraocular condition” such as active infections that could require medical intervention, as well as active inflammation:

- | |
|---|
| <ul style="list-style-type: none">• Active intraocular inflammation (grade trace or above) in the study eye.• Current vitreous hemorrhage in the study eye.• History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye.• History of idiopathic or autoimmune-associated uveitis in either eye.• Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. |
|---|

Id. at Supplemental Table A.

134. The PIER Study therefore explicitly teaches the first two claimed exclusion criteria – “active intraocular inflammation” and “actual ocular or periocular infection.” *Id.*

9. Prior Art Regarding Efficacy of Aflibercept

135. In my opinion, a POSA, having knowledge of the prior art references discussed above, was also aware of the results of various Phase 1 and Phase II trials of aflibercept for AMD and DME from other available publications at the time. For example, a POSA was aware of a Regeneron May 1, 2006 Press Release (“2006 Press Release”) that discloses a six-week Phase 1 trial of VEGF Trap-Eye involving a “single intravitreal injection of 0.05, 0.15, 0.5, 1, 2, or 4 milligrams (mg) of VEGF Trap” for treatment of AMD. Ex. 1027, 2006 Press Release, 1. It reports “the two highest dose groups (2 mg and 4 mg) [showed] the mean improvement in BCVA [] 13.5 letters, with three of six patients gaining 15 or more letters.” *Id.*, 2; *see also* Ex. 1028, Nguyen 2009, at Fig. 3B (showing 14 letter ETDRS gain by Day 15 for 2.0/4.0mg). A POSA would have been aware of these results because they were made available on Regeneron’s website and reported at the ARVO annual meeting, which is one of the biggest and well-known associations for research in vision and ophthalmology. *Id.*, 1; *see also* Ex. 1028, Nyugen 2009 (further reporting results, confirming letter score measured by ETDRS).

136. Similarly, a POSA was aware of a Regeneron May 8, 2008 Press Release (“2008 Press Release”), which describes the Phase 2 clinical trial data concerning VEGF Trap-Eye for AMD, which “met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of

disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart).” Ex. 1029, 2008 May Press Release, 1-2. It reports that “[r]esults from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision.” *Id.* Based on these results, a POSA understood that aflibercept is at least as promising as ranibizumab in treating angiogenic eye disorders with Dixon further referring to aflibercept as the “most promising anti-VEGF investigational drug.” Ex. 1009, 1577.

137. Dixon also reported the Phase 1 results for aflibercept for treatment of DME, which were presented at the ARVO Annual Meeting in 2007. Five patients with DME were administered a single intravitreal injection of 4 mg VEGF Trap and monitored for 6 weeks following VEGF Trap administration. Ex. 1030, 2007 ARVO Abstract; Ex. 1009. As Dixon notes, BCVA increased by 9 letters at four weeks....” Ex. 1009, 1575; *see also*, Ex. 1030 (“Four patients had improvements in BCVA, ranging from 6 to 10 letters at 4 weeks post-injection.”).

138. Moreover, the Phase 2 results for aflibercept for DME were reported at the ARVO Annual Meeting in April, 2010. Ex. 1010, 2010 ARVO Abstract. In this trial, aflibercept was “dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses” through 6 months. Ex. 1005, 1. It was reported at the

ARVO Annual Meeting that “[a]t 6 months [24 weeks], the mean change in BCVA for each VTE arm ranged from +8.5 to +11.4 letters” and that “[n]o significant difference was noted among the VTE arms.” Ex. 1010.

B. Analysis

1. Claims 15 and 24 are Anticipated by Each of the 2009 Press Release and December 2010 Press Release

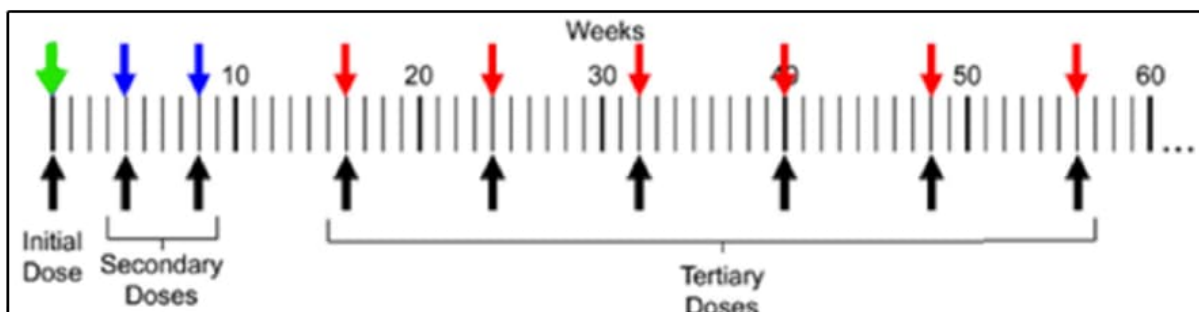
139. In my opinion each of the 2009 Press Release and December 2010 Press Release anticipates claims 15 and 24 of the '572 patent.

140. I understand that claim 15 recites a dosing regimen for treating a patient with diabetic macular edema in which a “single initial dose of 2 mg of aflibercept” is given, followed by “one or more secondary doses” administered every 4 weeks and “one or more tertiary doses” administered every 8 weeks thereafter. Unlike the other independent claims of the '572 patent, I note that claim 15 does not specify that a patient maintain or gain visual acuity. Claim 24 depends from claim 15 and recites that “only two secondary doses are given”. In other words, according to claim 24, the patient is administered three initial loading doses.

141. As discussed above, the 2009 Press Release discloses that “VEGF Trap-Eye is... in Phase 2 development for the treatment of Diabetic Macular Edema (DME). VEGF-Trap dosed at...2 mg every eight weeks after three monthly loading doses...is being compared to focal laser treatment.” Ex. 1005, 1. Likewise, the December 2010 Press Release discloses the study design and results of the same

Phase 2 clinical trial of aflibercept and states that one of the treatment arms included “patients with clinically significant DME ... receiv[ing] three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by ... every two months dosing...” Ex. 1006, 2.

142. In my opinion, this is the same dosing regimen recited by claims 15 and 24 – an initial dose at baseline and two secondary doses at weeks 4 and 8, followed by tertiary doses every 8 weeks, as shown below:



The 2009 Press Release and December 2010 Press Release disclose an initial dose (green), followed by two secondary doses (blue) (for a total of “three monthly doses”), further followed by tertiary doses (red) given “every eight weeks” or “every two months” through week 52.

143. Further, I understand that the Phase 2 dosing regimen disclosed in the 2009 Press Release and December 2010 Press Release was a method of “treating” patients with DME as the term was understood by a POSA. This is because based on its use in a Phase 2 trial to confirm safety and efficacy as well as positive results reported in prior trials for the treatment of DME, the administration of aflibercept

according to the Phase 2 dosing regimen disclosed in the 2009 Press Release and December 2010 Press Release was for the purpose of improving or providing a beneficial effect.¹ *Id.* Moreover, as discussed above, it was common knowledge at the time that VEGF Trap-Eye and aflibercept were the same drug, and thus, the use of VEGF Trap-Eye disclosed in the 2009 Press Release and December 2010 Press Release inherently and necessarily disclosed the use of aflibercept.² *See*, Exs.1011-13.

¹ In the '338 FWD, '601 ID, and '681 ID, the Board found that administering a compound—the recited VEGF antagonist—“to [a] patient for the purpose of improving or providing a beneficial effect on their angiogenic eye disorder” satisfies the “treating” portion of the preamble. Exs.1011-13.

² It was understood and known at the time that VEGF Trap-Eye and aflibercept were the same drug, and the protein’s structure is inherent in it. *See* Section V.D. For instance, Dixon expressly teaches that aflibercept and VEGF Trap-Eye have the “same molecular structure” (Ex. 1009, 3), and Adis (Ex. 1015) refers to them interchangeably. *See also* Ex. 1011, '338 FWD, 34; Exs.1035-37. Additionally, Patent Owner has repeatedly indicated to the Patent Office that they are the same drug. *Compare* Ex. 1038, 3-5 (describing VIEW 1/2) with Ex. 1009, 1576

144. Accordingly, in my opinion, each of the 2009 Press Release and December 2010 Press Release anticipates claims 15 and 24 of the '572 patent.

2. Claims 1-5, 8-11, 16-17, and 20-21 (Generic/DME Results Claims) Are Anticipated by the December 2010 Press Release

145. In my opinion, the December 2010 Press Release anticipates claims 1-5, 8-11, 16-17, and 20-21 of the '572 patent.

146. I understand that claims 1-5, 8-11, 16-17, and 20-21 are the “generic/DME Results Claims.” These claims recite the essentially same dosing regimen as claim 15, but also specifies the efficacy results of using the claimed dosing regimen. As discussed above, the December 2010 Press Release discloses a Phase 2 DME clinical trial of aflibercept in which the recited dosing regimen was used. I understand that the December 2010 Press Release further reports the visual acuity gain results from this Phase 2 DME clinical trial and anticipates all elements of the generic/DME Results Claims.

a) Claims 1 and 16

147. Claim 1 and claim 16 require the same loading and maintenance dosing regimen of claim 15, other than the identification of the disease to be treated (broader

(describing same); *See also* Ex. 1011, '338 FWD (reviewing Patent Owner's admissions).

angiogenic eye disorder in claim 1 v. DME claim 16) and additionally recite “the patient achieves a gain in visual acuity within 52 weeks following the initial dose.” The December 2010 Press Release reports that “[i]n Phase 2 study in DME, patients in all VEGF Trap-Eye Dose groups, including VEGF Trap-Eye dosed every two months, [following three monthly doses], maintained or increased vision gains through 52 weeks.” Ex. 1006, 1. Specifically, a mean gain of 9.7 letters was achieved by Week 52 for the “patients with clinically significant DME ... [who] received three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by ... every two months dosing...” The December 2010 Press Release summarizes the efficacy results as shown below:

	Laser	0.5mg monthly	2mg monthly	2mg every two months*	2mg PRN*
n	44	44	44	42	45
Mean change in visual acuity at week 24 versus baseline ¹ (letters)	2.5	8.6**	11.4**	8.5**	10.3**
Mean change in visual acuity at week 52 versus baseline (letters)	-1.3	11.0**	13.1**	9.7**	12.0**
*Following 3 initial monthly doses					
**p<0.01 versus laser					
¹ Primary endpoint					

Ex. 1006, 3.

148. Thus, the December 2010 Press Release discloses the claimed dosing regimen for treating angiogenic eye disorder, specifically DME, and “a gain in visual acuity within 52 weeks following the initial dose.” Claims 1 and 16 are anticipated by the December 2010 Press Release.

b) Claim 2

149. I understand that claim 2 depends from claim 1 and recites that “the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” A POSA would have understood that the visual acuity gains disclosed in the December 2010 Press Release were in BCVA according to ETDRS score, which the December 2010 Press Release describes as the “standard chart used in research to measure visual acuity.” Ex. 1006, 3. This is consistent with my understanding that measuring visual acuity gains in BCVA according to ETDRS was and still is standard in ophthalmology research. In fact, a POSA would have been aware that the DME trial disclosed in the December 2010 Press Release measured the visual acuity gains in BCVA according to the ETDRS score. *See, e.g.*, Ex. 1031, Do 2011, 1819 (“Patients in the 4 VEGF Trap-Eye groups experienced mean visual acuity benefits ranging from +8.5 to +11.4 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters”).

150. Thus, in my opinion, the December 2010 Press Release anticipates claim 2.

c) Claims 3, 8, 10, 17, and 21 and Claims 4, 9, and 20

151. Claims 3, 8, 10, 17, and 21 depend from claims 2 and 16 and additionally require that “the patient gains at least [7, 8, or 9] letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study

(ETDRS) letter score” within Week 52. Claims 4, 9, and 20 require the gain within 24 weeks.

152. As discussed above, the December 2010 Press Release reports that a mean gain of 9.7 letters was achieved by Week 52. Ex. 1006, 2-3. I note that the December 2010 Press Release also reports that a mean gain of 8.5 letters was achieved by Week 24:

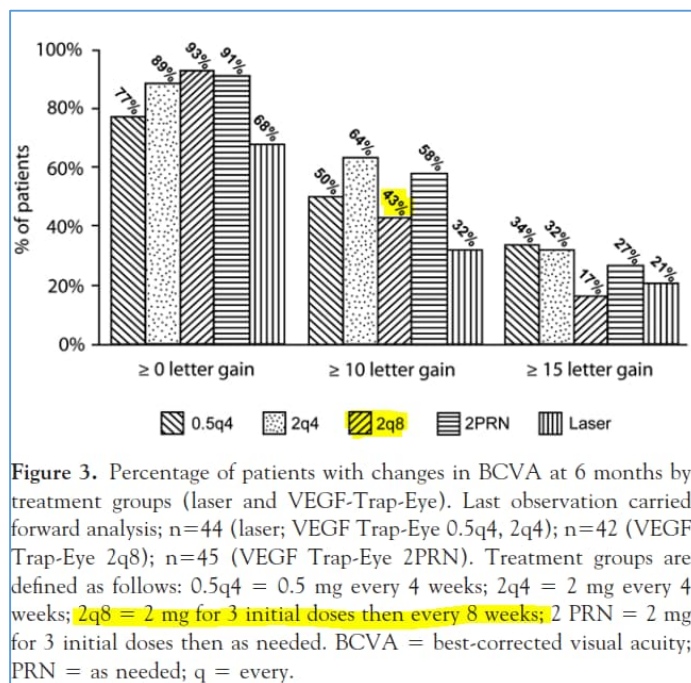
	Laser	0.5mg monthly	2mg monthly	2mg every two months*	2mg PRN*
n	44	44	44	42	45
Mean change in visual acuity at week 24 versus baseline ¹ (letters)	2.5	8.6**	11.4**	8.5**	10.3**
Mean change in visual acuity at week 52 versus baseline (letters)	-1.3	11.0**	13.1**	9.7**	12.0**

*Following 3 initial monthly doses
**p<0.01 versus laser
¹ Primary endpoint

Ex. 1006, 3; *see also* Ex. 1031, Do 2011, Figure 3. In my opinion, a POSA would have understood that the reported mean gain of 8.5 letters necessarily indicated that there were at least **some** patients who had a gain in visual acuity of at least 9 letters, given that letters scores are measured in whole letters and the mean is the average of these scores.³ In fact, Do 2011 reporting on the detailed results of the Phase 2 DME study confirms that at least 43% of the patients who received three initial monthly

³ I note that this is the same data that is disclosed in the '572 patent. *See*, Ex. 1001, Table 2 in Example 5.

doses followed by doses every 8 weeks achieved a gain of at least 10 letters by Month 6 (i.e. week 24) as shown below.



Ex. 1031, Do 2011, Figure 3. Accordingly, in my opinion, the December 2010 Press Release anticipates claims 3, 8, 10, 17, and 21 and claims 4, 9, and 20.

d) Claims 5 and 11

153. I understand that claim 5 and 11 depend from claims 3 and 10 respectively and additionally recite that “only two secondary doses are administered to the patient.” As discussed above, the December 2010 Press Release anticipates claims 3 and 10, and the additional limitation of “two secondary doses” is disclosed in the December 2010 Press Release as part of the regimen’s use of three initial monthly doses.

3. Claims 26-30 (AMD Results Claims) Are Anticipated by the November 2010 Press Release

154. Claims 26-30 are the “AMD Results Claims” that recite the same loading and maintenance doses of claim 15, but differ only with respect to the identification of the disease to be treated (e.g., AMD v. DME) and the efficacy limitations requiring the methods to be “as effective” as monthly administration of ranibizumab. In my opinion, the November 2010 Press Release discloses the Phase 3 AMD trial design of aflibercept along with the associated efficacy results and anticipates claims 26-30.

a) Claims 26-28

155. I understand that claim 26 recites the same dosing regimen as claims 1 and 15, but further recites that the claimed method is “as effective in achieving a gain in visual acuity” as monthly administration of 0.5 of ranibizumab in AMD patients “at 52 weeks.” Dependent claim 27 specifies that only two secondary doses are given, as disclosed in the November 2010 Press Release. Ex. 1007, 3-4. Dependent claim 28 recites the gain is measured using ETDRS, as also disclosed in the November 2010 Press Release.

156. I understand that the November 2010 Press Release discloses Phase 3 AMD clinical trials of aflibercept in which “VEGF Trap-Eye was evaluated for its effect on maintaining and improving vision when dosed as an intravitreal injection on a schedule of ... 2mg every two months (following three monthly loading doses),

as compared with intravitreal ranibizumab administered 0.5 mg every month during the first year of the studies.”⁴ Ex. 1007, 3. This is the same dosing regimen recited by claims 26-28.

157. The November 2010 Press Release reports a mean improvement/gain in visual acuity between 7.9 and 8.9 letters for patients receiving bimonthly doses of 2 mg aflibercept after three initial monthly doses at Week 52, which it identifies as statistically non-inferior to monthly ranibizumab. Ex. 1007, 4. Notably, these are the same values as reported in Table 1 of the ’572 patent, which also identifies these results as non-significantly different than the reported ranibizumab results of between 8.1 and 9.4 visual acuity gains.⁵ Ex. 1001, col 13:5-35. The November 2010 Press Release summarizes the efficacy results as shown below:

⁴ As noted above in Section V.D., it was understood at the time that VEGF Trap-Eye and aflibercept were the same drug.

⁵ For purposes of this expert declaration only, I have been asked by counsel for Petitioner to assume that monthly administration of 0.5 mg ranibizumab produces a mean gain of visual acuity between 8.1-9.4 letters and prevents a loss of more than 15 letters for 94.4 % of patients at week 52, which is the result reported in Table 1 of the ’572 patent.

	Ranibizumab 0.5mg monthly	VEGF Trap-Eye 0.5mg monthly	VEGF Trap-Eye 2mg monthly	VEGF Trap-Eye 2mg every 2 months
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
VIEW 1	94.4%	95.9%**	95.1%**	95.1%**
VIEW 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value versus ranibizumab 0.5mg monthly)***				
VIEW 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
VIEW 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS)
* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart				
** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)				
*** Test for superiority				
NS=non-significant				

Ex. 1007, 4.

158. The November 2010 Press Release also discloses that “VEGF Trap-Eye dosed every two months [after three monthly doses], *successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month*. The primary endpoint was statistical non-inferiority in...patients who *maintained (or improved) vision over 52 weeks compared to ranibizumab.*” Ex. 1007, 1.

159. Moreover, as was the case for the anticipation of claims 15 and 24 by the 2009 Press Release and December 2010 Press Release, the administration of aflibercept according to the November 2010 Press Release was a method of “treating” patients with AMD as the term was understood by a POSA, given its use in a Phase 3 trial to confirm efficacy for regulatory approval and a number of successful past clinical trials. Accordingly, the November 2010 Press Release anticipates claims 26-28.

b) Claims 29-30

160. Claim 29 recites the same dosing regimen as claims 1, 15, and 26 but further recites that the claimed method is “as effective in maintaining visual acuity” as monthly administration of 0.5 of ranibizumab in AMD patients “at 52 weeks.” Claim 30 further specifies that such maintenance “means loss of less than 15 letters” BCVA as measured by ETDRS. Accordingly, in my opinion, the November 2010 Press Release only need to disclose that its dosing regimen prevented loss of more than 15 letters BCVA in some patients in order to be “as effective in maintaining visual acuity” as monthly ranibizumab at 52 weeks.

161. As discussed above, the November 2010 Press Release states that “[m]aintenance of vision was defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS eye chart” in the Phase 3 AMD trial, and that maintenance was achieved. Ex. 1007, 2. The November 2010 Press Release reports that 95.1-95.6% of patients who received bimonthly doses of 2mg aflibercept followed by three initial monthly doses achieved maintenance of vision at week 52, which is comparable to 94.2% reported for the monthly ranibizumab arm. The November 2010 Press Release further discloses a mean improvement/gain in visual acuity between 7.9 and 8.9 letters for patients who have received bimonthly doses of 2 mg aflibercept after three initial monthly doses at week 52. *Id.*, 4. This shows that the claimed dosing regimen disclosed in the November 2010 Press Release not only

maintained visual acuity, but also produced additional visual acuity gains. *Id.* Therefore, in my opinion, the November 2010 Press Release anticipates claims 29-30.

4. Claims 1-5, 8-11, and 26-30 (Generic/AMD Results Claims) Are Rendered Obvious by Dixon Alone or In View of the 2006 Press Release

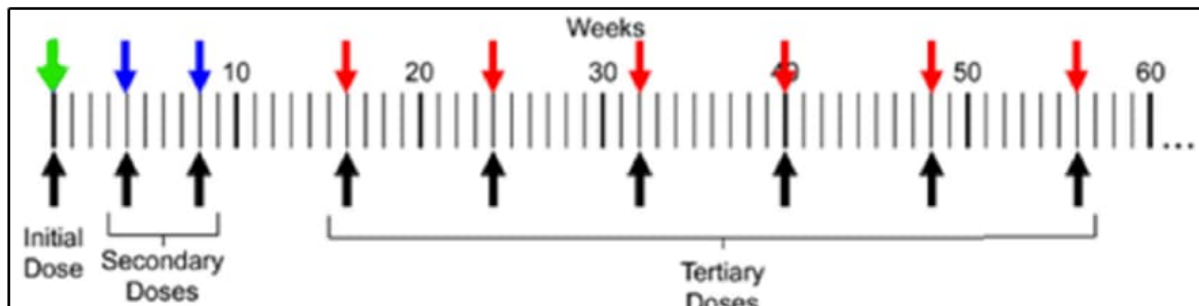
162. In my opinion, Dixon alone or in view of the knowledge of a POSA renders obvious claims 1-5, 8-11, and 26-30.

163. In my opinion, Dixon teaches administering the recited dosing regimen to a patient for the purpose of treating an angiogenic eye disorder, including AMD. Ex. 1009. Dixon teaches that “VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development for the treatment of neovascular AMD by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA)...” Ex. 1009, 1573, 1576-77.

164. As to the recited dosing regimen, Dixon discloses that the Phase III study “will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of... 2.0 mg at an 8 week dosing interval (following three monthly doses)...” Ex. 1009, 1576.⁶ As shown below in an annotated version of the sole '572 Figure, Dixon discloses an initial dose (green), followed by two secondary doses (blue) (for a total

⁶ As discussed in Sections V.D., Dixon expressly teaches that aflibercept and VEGF Trap-Eye have the “same molecular structure” Ex. 1009, 1575.

of “three monthly doses”), further followed by tertiary doses (red) given at an “8 week dosing interval”:



165. While Dixon does not expressly disclose the “results limitations” in independent claims 1, 26, or 29 or their dependents, in my opinion, it renders them obvious alone or in view of the knowledge of a POSA regarding aflibercept efficacy as further discussed below.

a) Claim 1

166. Independent claim 1 recites that “the patient achieves a gain in visual acuity within 52 weeks following the initial dose.” As an initial matter, I note that claim 1 and all of the Results Claims other than claims 26-30, recite no requirement that a patient maintain any visual acuity gain for a set duration. They only require that the patient “achieves the gain within” the recited time period at any point. Specifically, claim 1 requires achieving the gain within 52 weeks.

167. Moreover, there is no requirement that every patient achieve the recited gain, only that such gains would be obvious for some patients – i.e., for “a patient” as recited in the claims.

168. First, POSAs knew from the Phase I trial of aflibercept reported in the 2006 Press Release that a single 2 mg dose in AMD patients produced a “mean improvement in BCVA [] 13.5 letters, with three of six patients gaining 15 or more letters” at six weeks. Ex. 1027, 1. The described gain is “within” 52 weeks, and thus in my opinion, a POSA would have expected a visual acuity gain within 52 weeks for some patients from administration of the first dose in Dixon’s Phase III dosing regimen alone.

169. Moreover, in my opinion, POSAs understood that the secondary endpoint of the VIEW 1 study, which used the Phase III dosing regimen of Dixon and described in Dixon was the “proportion of patients who gained at least 15 letters of vision at week 52” as measured by ETDRS. Ex. 1005, 1. In my opinion, a POSA would have found a visual acuity gain within the first 52 weeks for some patients receiving Dixon’s Phase III dosing regimen obvious and expected based on this knowledge. I incorporate herein my discussion of claims 3-4 and 8-10, which address specific visual acuity gains and further show the obviousness of claim 1.

b) Claim 2

170. Claim 2 depends from claim 1 and recites that “the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” Dixon describes the visual acuity gains as BCVA according to ETDRS score throughout, and ETDRS is the

“standard chart used in research to measure visual acuity.” *See, e.g.* Ex. 1009, 1576; *see also* Section X.B.3.

c) Claims 3-4 and 8-10

171. Claims 3-4 and 8-10 additionally require that “the patient gains at least [7, 8, or 9] letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score” within 52 weeks or 24 weeks. Thus, I understand that if it was obvious to a POSA that a visual acuity gain of 9 letters would be achieved at least for some patients within 24 weeks, all of these claims are rendered obvious.

172. First, as discussed above in claim 1, a POSA would have reasonably expected a gain of at least 15 letters for at least some patients within the first six weeks of treatment under Dixon’s Phase III dosing regimen (i.e., at least after the first dose) based on the fact that the reported Phase 1 results for aflibercept showed 15 letter gains from a single 2 mg injection. *See* Section X.B.4.(a). In my opinion, this is sufficient to render these claims obvious. *Id.*

173. Second, as discussed further with regard to claims 26-28, Dixon reports the Phase II results showing that AMD patients who received four initial monthly doses followed by PRN dosing received only an average of 1.6 additional injections through 52 weeks (for a total of ~5.6 doses in a year on average). Dixon discloses

that these patients achieved a mean of 9 letter gains, with 29% gaining greater than 15 letters, by 52 weeks. Ex. 1009, 1576.

174. Based on this teaching, a POSA would have reasonably expected that at least some AMD patients, including those that achieved at least 15 letter gains, would have achieved a 9 letter visual acuity gain or more at some point during the first 24 weeks treatment, especially in view of its knowledge of the effectiveness of a single dose as discussed above and the Phase II results. This is because Dixon's loading/maintenance schedule would result in 8 overall doses during the year—two more doses than had been shown to produce 15 letter gains in almost 1 in 5 patients in the Phase II results.

d) Claims 5 and 11

175. Claim 5 and 11 depend from claims 3 and 10 respectively and additionally recite that “only two secondary doses are administered to the patient.” Dixon renders obvious claims 3 and 10 and discloses the use of three monthly loading doses—an initial dose and “only two secondary doses.” Ex. 1009, 1576 (*following three monthly doses*)....”) therefore renders obvious claims 5 and 11.

e) Claims 26-28

176. Claim 26 recites the same dosing regimen as claims 1 and 15, but further recites that the claimed method is “as effective in achieving a gain in visual acuity” as monthly administration of 0.5 of ranibizumab in AMD patients “at 52

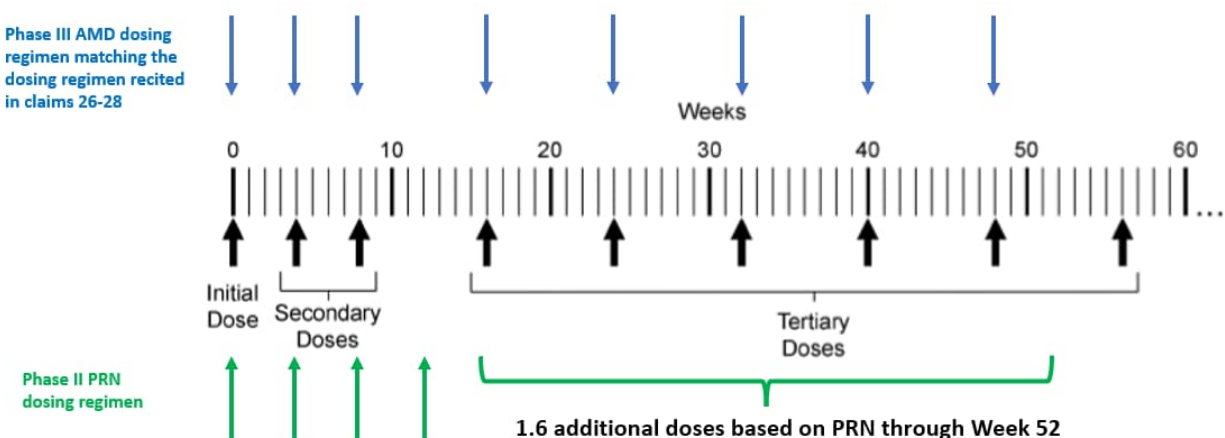
weeks.” Dependent claim 27 specifies that only two secondary doses are given, as disclosed in Dixon. *See* Sections X.A.4 and B.3. Dependent claim 28 recites the gain is measured using ETDRS, as also disclosed in Dixon. *Id.*

177. For the purposes of this section only, I have been asked by counsel for Petitioner to be “as effective” as monthly ranibizumab, a patient must achieve a mean gain of visual acuity between 8.1-9.4 letters, as reported in Table 1 of the ’572 patent. Ex. 1001, col. 13:5-35. I also note that a POSA would understand that an individual patient in a clinical study may not achieve the mean gain as reported.

178. As discussed with regard to claims 1, 3-4, and 8-10, Dixon renders obvious a substantially higher gain of visual acuity than 8.1-9.4 letters for some patients. Moreover, Dixon discloses that in the Phase II AMD trial, AMD patients who were administered four initial monthly doses, followed by PRN dosing, received only an average of 1.6 additional injections beyond the initial monthly doses through 52 weeks (for a total of ~5.6 doses in a year on average) (“Phase II PRN Dosing Regimen”). Ex. 1009, 1576. These patients achieved a mean of 9 letter gains, with 29% gaining greater than 15 letter gains, by 52 weeks. *Id.*

179. Dixon further discloses the Phase III AMD trial dosing regimen in which 2 mg of aflibercept was administered “at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab administered every 4 weeks.” (“Phase III AMD Dosing Regimen”) *Id.*

180. As noted above, aflibercept was known as the “most promising” anti-VEGF drug under clinical investigation. Ex. 1009, 1577. Thus, in my opinion, a POSA would have reasonably expected that when aflibercept is administered according the recited dosing regimen of monthly administration followed by bi-monthly dosing as used in Dixon’s Phase III AMD Dosing Regimen, at least some AMD patients would have achieved the gains that are comparable to the gains achieved by monthly administration of ranibizumab. This is because under the Phase II PRN Dosing Regimen, the patients who achieved a mean of 9 letter gains, with 29% gaining greater than 15 letters, by 52 weeks received 4 doses through week 12, and only 1.6 additional doses through week 52. In comparison, Dixon’s Phase III AMD Dosing Regimen required 4 doses through week 16—only a 4 week difference—and additional 4 doses through week 52. A comparison of the two dosing regimens is shown below:



181. Thus, in my opinion, Dixon's Phase III AMD Dosing Regimen recited in claims 26-28 would have resulted in three initial monthly doses, and 8 overall doses during the year—at least two more doses than the Phase II PRN Dosing Regimen that had been shown to produce 15 letter gains in almost 1 in 5 patients by week 52. Ex. 1009, 1576. In my opinion, given that 29% of patients followed the Phase II PRN Dosing Regimen had greater than 15 letter gains by 52 weeks, a POSA would have reasonably expected at least similar gains, and substantially higher gains than just 8.1-9.4 letters achieved by ranibizumab, in view of the at least two additional doses administered through Week 52.

182. Moreover, a POSA would have found it obvious to modify the Dixon's Phase III AMD Dosing Regimen to include additional initial doses, for the same reasons discussed in relation to claim 25. In other words, adding more initial doses would have been routine for a POSA. Modifying Dixon's Phase III AMD Dosing Regimen to include four initial doses would bring it further closer to the Phase II regimen, but would also include five additional doses during the remaining 52 week period as compared to only the 1.6 mean doses given in the Phase II PRN Dosing Regimen. This would result in at least three more doses than the Phase II PRN Dosing Regimen, which would only serve to increase a POSA's reasonable expectation of producing a gain as effective as monthly administration of ranibizumab.

f) Claims 29-30

183. Claim 29 recites the same dosing regimen as claims 1, 15, and 26 but further recites that the claimed method is “as effective in maintaining visual acuity” as monthly administration of 0.5 of ranibizumab in AMD patients “at 52 weeks.” Dependent claim 30 further specifies that such maintenance “means loss of less than 15 letters” BCVA as measured by ETDRS. Accordingly, I understand that a POSA would need only to find it obvious that Dixon’s dosing regimen merely prevented loss of more than 15 letters BCVA in order to be “as effective in maintaining visual acuity” as monthly ranibizumab at 52 weeks. As discussed above, a POSA would have found it obvious that Dixon’s dosing regimen would produce visual acuity *gains*, not just maintenance above a loss of 15 letters. Moreover, a POSA would have expected the maintenance of vision to be comparable to monthly ranibizumab because VEGF-Trap/aflibercept had “higher binding affinity” and likely “longer duration of effect in the eye” than ranibizumab. Ex.1009, 1577. Thus, in my opinion, for the same reasons recited above, these claims are obvious.

5. Claims 16-17, and 20-21 (DME Results Claims) Are Rendered Obvious by the 2009 Press Release Alone or in View of the 2007 ARVO Abstract, Dixon, and/or the 2010 ARVO Abstract (collectively, “Section X.B.5 References”)

184. As discussed in Section X.B.1., the 2009 Press Release discloses every limitation of claim 15. I understand that the DME Results Claims depend from claim 15. Claim 16 additionally recites a “gain in visual acuity within 52 weeks,” while

dependent claim 17 specifies the gain is at least 9 letters of BCVA in ETDRS. Dependent claim 21 recites the gain is at least 8 letters. Claim 18 depends from claim 17 (a gain of at least 9 letters) and recites the patient achieves the gain “within 24 weeks,” not 52. Accordingly, in my opinion, the 2009 Press Release need only render obvious a gain of 9 letters within 24 weeks to render all of the DME Results claims obvious.

185. In my opinion, a POSA would have found it obvious and expected that at least some patients, when treated via the 2009 Press Release dosing regimen, would achieve a 9 letter gain, which was modest compared to known gains for aflibercept and other anti-VEGF agents. Ex. 1001, cl. 1. The Results Claims do not require the dosing regimen to apply to all patients populations in a one-size-fits-all approach. Rather, the claims are directed to a “method for treating diabetic macular edema in *a* patient.” Nor do they require that a patient maintain any visual acuity gain for a set duration—only that the patient “achieves the gain *within*” the recited time period—here 24 or 52 weeks.

186. First, the 2009 Press Release discloses that, in the context of the VIEW 1 study for AMD, which involved the use of three monthly loading doses followed by 8-week dosing intervals, a secondary endpoint is the “proportion of patients who gained at least 15 letters of vision at week 52” as measured by ETDRS. Ex. 1005, 1. As to the Phase 2 trial for the treatment of DME, the 2009 Press Release explains

that the “primary efficacy endpoint evaluation is mean improvement in visual acuity at six months.” *Id.*

187. In my opinion, a POSA would have found it obvious that the Phase 2 trial for treatment of DME, involving the same number of initial loading doses as the VIEW 1 study, would be expected to produce similar improvement ***for at least some patients*** as was expected to be produced in the VIEW 1 study. In other words, in my opinion, there would be nothing unexpected about a patient losing no less than or gaining at least 15 letters of vision (even if others did not) to a POSA.

188. This is particularly so because DME and AMD share a similar mechanism of action. As noted in Section V, the mechanism of action for both AMD and DME involves the formation of abnormal blood vessels in the macula, which can leak fluid and cause swelling and damage to the macula. In AMD, the abnormal blood vessel formation is called choroidal neovascularization (CNV), which occurs when new blood vessels grow beneath the retina and leak fluid or blood, causing damage to the macula. In DME, the abnormal blood vessel formation is called diabetic retinopathy, which is caused by high blood sugar levels damaging the blood vessels in the retina, leading to the formation of leaky blood vessels. In sum, while the underlying causes of AMD and DME may differ, their mechanism of action and treatment approaches share similarities in targeting and inhibiting abnormal blood vessel formation and leakage in the macula. Indeed, the claims and specification of

the '572 patent refer to AMD and DME as part of “angiogenic eye disorders,” further confirming similarity in their mechanisms of action and treatment strategies. Accordingly, a POSA would have recognized and expected that a treatment method that works for AMD would likely work for DME and achieve a similar efficacy outcome.

189. Moreover, as reported in the ARVO 2007 Abstract and Dixon, it was known from the Phase I trial of aflibercept that a single 4 mg dose in DME patients produced a “9 letters [gain in EDTRS] at four weeks....,” well before the 24 week time frame recited in claim 20. Ex. 1009, 1575; Ex. 1030 (“Four patients had improvements in BCVA, ranging from 6 to 10 letters at 4 weeks post-injection.”). Based on this understanding, a POSA would have reasonably expected that the same gain would be produced by an initial set of three 2 mg loading doses instead of a single 4 mg dose, particularly given the successful use of initial loading doses in the context of AMD trials. See Ex. 1009.

190. Finally, in my opinion, a POSA would have found their expectation further confirmed by data reported in April 2010 at the ARVO Annual Meeting and in the 2010 ARVO Abstract. It was reported there that POSAs knew that that “[a]t 6 months [i.e. 24 weeks], the mean change in BCVA for each VTE arm ranged from +8.5 to +11.4 letters” gains had been achieved in the DME clinical trials described in the 2009 Press Release. Ex. 1010, 1. This would confirm a POSA’s reasonable

expectation that the 2009 Press Release regimen would produce 9 letter gains by 24 weeks. Therefore, it is my opinion that claims 16-17, and 20-21 are rendered obvious by the 2009 Press Release alone or in view of the knowledge of a POSA.

6. Claims 6-7 and 12-13 (Aflibercept Formulation) Are Rendered Obvious by Each of Dixon in View of Hecht, Dixon in View of the 2006 Press Release and Hecht, and the December 2010 Press Release in View of Hecht

191. I understand that claims 6-7 and 12-13 depend from claims 3 and 10 respectively and recite that the aflibercept is formulated as “an isotonic solution” and with a “nonionic surfactant.” As discussed in Sections X.B.2 and 4-5, claims 3 and 10 are anticipated by the December 2010 Press Release and rendered obvious by Dixon in view of the 2006 Press Release. In my opinion, a POSA would have found the use of an isotonic formulation and nonionic surfactant in the disclosed formulation in these primary references obvious.

192. First, Dixon teaches that aflibercept is “formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye.” Ex. 1009, 1575. Dixon’s teaching is consistent with how a POSA would have understood the aflibercept formulation in each of the prior art references discussed throughout this declaration. In particular, it is my opinion that a POSA would have understood that a non-isotonic formulation would irritate a patient’s eye, and would expect an isotonic formulation to be used. This was common and known practice among practitioners then and now.

193. Hecht further confirms this understanding. Hecht teaches the principles of formulation for ophthalmic solutions and specifically notes that such solutions must be “formulated to be sterile, isotonic and buffered for stability and comfort.” Ex. 1016, 1568; *Id.*, 1571 (“[I]sotonicity always is desirable and particularly is important in intraocular solutions.”). In my opinion, a POSA would have been motivated to make the aflibercept solution disclosed in the primary references isotonic to avoid irritation and would have a reasonable expectation in doing so, particularly given aflibercept was already known to be administered intravitreally in various clinical trials with success.

194. Similarly, Hecht teaches that non-ionic surfactants are the “least toxic to ophthalmic tissues,” “[a]id in achieving solution clarity,” and can serve as “cosolvents to increase solubility.” Ex. 1016, 1571. It was also known that such surfactants stabilize proteins such as aflibercept. *See* Ex. 1032, Randolph, 159. Thus, in my opinion, a POSA would have found it obvious that the formulations disclosed in the primary references discussed here would include a nonionic surfactant, would have been motivated to formulate aflibercept with a nonionic surfactant to achieve the known benefits, and would have had a reasonable expectation of success because aflibercept was already known to be administered intravitreally and had been formulated with a non-ionic surfactant for other uses. *See* Ex. 1033, Fraser, 1115.

7. Claims 18-19 and 22-23 (Aflibercept Formulation) Are Rendered Obvious by Each of the December 2010 Press Release in View of Hecht, and the 2009 Press Release in View of the Section X.B.5 References and Hecht

195. Claims 18-19 and 22-23 depend from claims 17 and 21 respectively and recite the same “an isotonic solution” and “nonionic surfactant” limitations addressed above. As set out in Sections X.B.2 and 5, claims 17 and 21 are anticipated by the December 2010 Press Release and rendered obvious by the 2009 Press Release alone or in view of the Section X.B.5 references disclosing the efficacy of aflibercept for DME. For the same reasons as those in Section X.B.6., which I incorporate herein, these references in combination with Hecht render claims 18-19 and 22-23 obvious.

8. Claim 14 (Exclusion Criteria) Is Rendered Obvious by Each of Dixon, and the December 2010 Press Release Alone or In View of the CATT Study and/or PIER Study

196. Claim 14 depends from claim 1 and recites “wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection.” As I discussed in Section VIII.B., I have been asked to assume that the exclusion criteria should not be given patentable weight. Accordingly, these claims are rendered obvious for the same reasons as set forth in Sections X.B.2 and 4.

197. Even if the exclusion criteria are given patentable weight, it is still my opinion that claim 14 would have been obvious to a POSA. The recited exclusion criteria were well known in the art and disclosed to a POSA.

198. Specifically, a POSA was aware of the CATT and PIER Studies (Exs. 1020, 1021-26) described above in Section X.A.8., which included exclusion criteria for clinical trials of the leading intravitreally injected anti-VEGF treatments at the time —bevacizumab (Avastin[®]) and ranibizumab (Lucentis[®]). The exclusion criteria disclosed in these studies are the same as those claimed by the '572 patent, as is shown in Table 1 above in Section X.A.8. Applying these exclusion criteria in combination with the prior art disclosures and teaching discussed in Sections X.B.2 and 4 above renders the claimed method obvious.

199. Moreover, the '572 patent does not identify anything specifically unique or novel about the combination of the exclusion criteria together or with the claimed method. Instead, they are merely listed along with 34 other exclusion criteria in the specification, without any further discussion. These exclusion criteria are basic safety precautions associated with intravitreal injections of anti-VEGF agents.

200. Finally, a POSA would have been motivated to adopt the exclusion criteria in order follow the standard of care, as set out above, as well as to solve a problem that references such as the 2009 Press Release and Dixon discuss directly.

For instance, Dixon discloses that a problem exists in the art with dosing regimens involving intravitreal injections, such as those disclosed in conjunction with the VIEW1/2 studies: “Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.” This was a known problem in the art, as applicants themselves acknowledged during prosecution of the ’681 patent, which I understand is a related patent to ’572 patent in the same patent family. Ex. 1055, June 25, 2018 Applicant Remarks at 8 (“[monthly] treatment protocol... subjects the patient to potential adverse effects such as infection with each treatment event”); *see also* Ex. 1034 (Lucentis Label) at 1 (listing endophthalmitis and intraocular inflammation as risks); Ex. 1021, PIER, 239-240 (same); Ex. 1005, 2009 Press Release (addressing same).

201. POSAs were aware of both risks. For example, the PIER study describes endophthalmitis and intraocular inflammation as having a “hypothesized or documented relationship to ranibizumab” and set out procedures to limit the risk. Ex. 1021, 247. Similarly, both endophthalmitis and intraocular inflammation were acknowledged as risks on, for instance, the 2006 label for ranibizumab (Lucentis®), one of the two leading anti-VEGF treatments at the time (Ex. 1034, 1), as well as the 2011 Eylea label. Ex. 1059.

202. Endophthalmitis is a risk for anti-VEGF injections because they involve penetration by a small gauge needle into the eye, and thus there is a risk of

bringing flora from the eye (“ocular”) or surrounding area (“periocular”) into the vitreous cavity. As noted by Dixon, this can potentially cause endophthalmitis, a severe and potentially blinding condition. Endophthalmitis was “the most feared” consequence of medical procedures that penetrate the eye. Ex. 1060, Jaffe, 349. Injecting with an active infection in or around the eye substantially increases that risk because of the potential increase in available flora. *See also* Ex. 1061, Steps for a Safe Intravitreal Injection Technique (2009).

203. Similarly, prior studies of anti-VEGF intravitreal injections demonstrated that a primary complication from such injections was intraocular inflammation. Ex. 1021, PIER Study. In my opinion, excluding patients with pre-existing intraocular inflammation from receiving an intravitreal injection that was known to aggravate such inflammation was part of the standard of care for this reason. Applying the recited exclusion criteria disclosed in PIER and CATT Study would only increase a POSA’s expectation of success in treatment. Ex. 1021, PIER Study; Ex. 1020, CATT Study; Ex. 1034, Lucentis Label, 1.

9. Claim 25 (Five Initial Doses) is Rendered Obvious by the 2009 Press Release Alone or in View of Shams or Elman 2010

a) Claim 25 is Rendered Obvious by the 2009 Press Release Alone or in view of Shams

204. Claim 25 depends from independent claim 15 and specifies that “four secondary doses are administered to the patient,” meaning the dosing regimen

consists of five initial monthly doses, followed by 8-week maintenance dosing (no “results limitations” are recited). I understand that this is the same dosing regimen recited in the DME claims challenged in Petitioner’s ’601 IPR (IPR2023-00739), in which I also submitted an expert declaration. Similar to the DME claims in Petitioner’s ’601 IPR, it is my opinion that claim 25 of ’572 patent is rendered obvious by the 2009 Press Release alone or in view of Shams or Elman 2010.

205. First, the 2009 Press Release teaches that Regeneron was beginning clinical trials studying the efficacy of aflibercept to treat DME via three different dosing regimens for 2 mg VEGF Trap-Eye. Ex. 1005. Specifically, the press release discloses that aflibercept is “in Phase 2 development for the treatment of Diabetic Macular Edema (DME)” with a dose “at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses....” *Id.*

206. As discussed in Section V.E, the primary problems associated with monthly injections were patient burden and injection complications. Thus, a POSA reading the 2009 Press Release would have understood that Regeneron was pursuing multiple different dosing regimens with 2 mg of aflibercept to optimize dosing frequency for efficaciously treating DME with aflibercept, while minimizing the number of injections so as to minimize potential complications from repeated intravitreal injections.

207. A POSA would have also had a strong motivation to further optimize these dosing regimens to achieve the same two goals, especially given the success with other anti-VEGF agents in treating DME and knowledge from prior courses of treatment of DME with anti-VEGF agents. Ex. 1005.

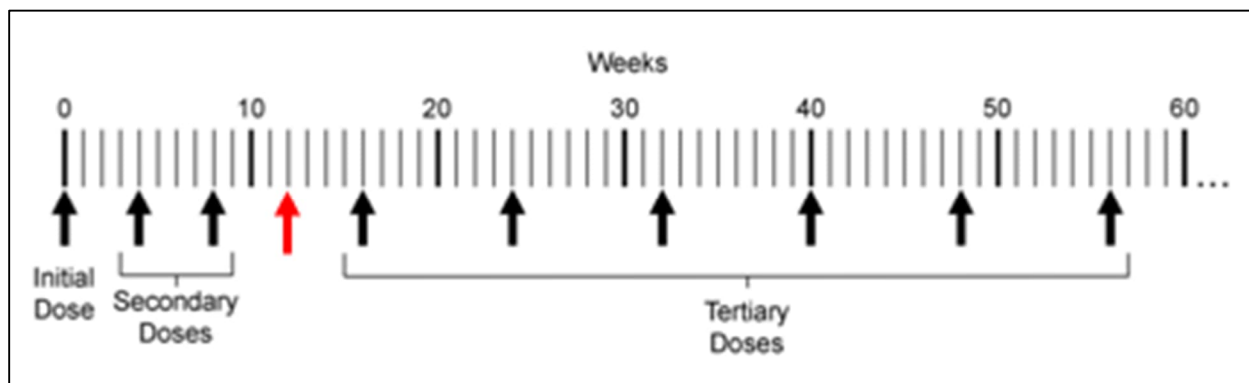
208. Moreover, as discussed in Section V.B, DME is characterized by leakage of fluid and blood and swelling from damage to blood vessels at the back inner wall of the eye (retina). The principal way to treat DME effectively in the first instance therefore was to “dry” the liquid and stop the leakage with a series of anti-VEGF injections. VEGF-antagonists are relatively short-acting compared to focal laser treatment, thus a series of initial injections are required.

209. Because there was a need to “dry” the retina before proceeding to reduce the frequency of injections, POSAs would have thus sought, through routine variation in the number of initial doses, to determine the optimal number of initial injections, before moving to eight-week dosing. Ex. 1018, Elman 2010.⁷ This is effectively what Elman 2010 studied.

210. In my opinion, including additional doses to treat DME would have been a matter of routine experimentation for a POSA. For instance, to arrive at the

⁷ As noted below, in Elman 2010, at least 78% of patients received a fifth initial loading dose in the ranibizumab + deferred laser group. Ex. 1018, 1067.

recited dosing regimen from the 2009 Press Release's disclosure of a regimen using three initial doses for DME, the only modification required is a *single* additional injection at week 12, as shown below in reference to the '572 patent's sole figure, which discloses a regimen involving three initial doses as disclosed in the press release:



Ex. 1001 (annotated figure). As can be seen above, the addition of a single dose at week 12 (red arrow) discloses the recited regimen.

211. Such variation is a routine part of practice in treating DME and other angiogenic diseases: it was a routine clinical practice to continue injections of other anti-VEGF agents on a regular 4 week interval until drying was complete, after which the dosing interval could be extended. There was nothing or new in the claimed dosing regimen in my opinion.

212. I find the disclosures of the '572 patent consistent with this understanding. The '572 patent nowhere identifies five loading doses as the proper or most efficacious number of loading doses for DR/DME (or any other indication).

Rather, the use of five loading doses is referenced in the '572 patent only as part of a list of twenty other variations on loading/maintenance dosing regimens that vary the number of initial doses—including two, three, four, five, six, seven, and eight loading doses spaced four weeks apart, as well as a dosing regimen of continuous doses spaced four weeks apart. Ex. 1001. The '572 patent states that “[a]ny of the foregoing administration regimens may be used for the treatment of....” DME, among a host of angiogenic eye disorders. Ex. 1001, 17:45-18:3. This mirrors exactly how a POSA would have evaluated the appropriate dosing regimen for an individual DME patient. A POSA would have considered it obvious to vary the number of initial loading doses disclosed in the art for the treatment of DME before moving to maintenance dosing for individual patients, including the use of five loading doses.

213. Shams further confirms this understanding. “[M]onthly dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist” was described in Shams as early as in 2006. Ex. 1017, 2. Shams explains that “a treatment schedule comprising an initial interval of administration of a therapeutic compound [an VEGF antagonist], followed by a subsequent, less frequent interval of administration of the therapeutic compound” allows “one to decrease subsequent doses of the therapeutic compound, while at the same time maintaining the therapeutic efficacy.”

Id., 22; *see also id.*, 5-6. It further explains that “[t]he specific time schedule [for administering doses] can be readily determined by a physician having ordinary skill in administering the therapeutic compound by routine adjustments of the dosing schedule within the method of the present invention [i.e. loading and maintenance dosing].” *Id.*, 23-24.

214. I also believe that POSAs would have had a reasonable expectation of success in pursuing such optimization. POSAs understood at the time that vascular leakage is a key characteristic of DME, which is caused by damage to the small blood vessels in the retina. POSAs also understood that vascular leakage in DME is dynamic and can fluctuate over time – the leakage may be persistent or intermittent, or may resolve on its own. This variability made it difficult to predict when DME will occur or worsen, and made it more challenging to manage DME effectively as compared to other angiogenic eye disorders.

215. Given this dynamic nature of vascular leakage in DME, POSAs would have understood that the principal strategy to treat DR and DME using anti-VEGF agents was to “dry” the retina completely in the first instance and then to maintain that state thereafter. Ex. 1018, Elman 2010, 1064-65. Phase 1 testing of a single 4 mg injection of aflibercept for DME, showed significant improvement—patient’s BCVA increased by 9 letters with a decrease of 79 μ m in retinal thickness as measured by OCT, which are indicative of a “dry” retina — but efficacy regressed

to a 3 letter improvement at six weeks without follow up. Ex. 1009, Dixon, at 1575. Thus, in my opinion, POSAs would have reasonably expected that continuing regular monthly loading doses beyond a single injection, until the retina was completely dry, would increase and maintain efficacy.

216. Furthermore, the clinical trials taught by the 2009 Press Release suggest that a regimen with more than three initial doses may be more successful and would be safe and tolerable at least for some individual patients, and less frequent dosing thereafter could be just as effective as continued initial dosing—further indicating a reasonable expectation of success. Specifically, as discussed above, the 2009 Press Release teaches (1) three or more initial monthly loading doses of aflibercept would be safe and tolerable, as all of the Phase 2 and 3 trials described in the 2009 Press Release included such initial monthly doses — a standard and proven safe regimen for anti-VEGF agents, and (2) secondary doses on a less frequent dosing interval (e.g., eight-week dosing and dosing on a PRN (pro ne rata; as needed) basis) would be sufficient to maintain the initial efficacy commonly seen with anti-VEGF agents. Ex. 1005. Thus, in my opinion, the 2009 Press Release alone or in combination with the teachings of Shams renders claim 25 obvious.

b) Claim 25 is Rendered Obvious by the 2009 Press Release in Combination with Elman 2010.

217. Similarly, in my opinion, the recited dosing regimen of claim 25 is obvious over the 2009 Press Release in combination with Elman 2010.

218. First, the 2009 Press Release teaches the use of 2mg of VEGF Trap-Eye to treat DME. Ex. 1005, 1. Specifically, the 2009 Press Release teaches that “VEGF Trap-Eye, an investigational drug, is being developed ... for the potential treatment of eye diseases, including ... diabetic macular edema (DME)...” The 2009 Press Release, 1. It further describes Phase 2 clinical trial for DME with a dosing regimen of 2 mg aflibercept administered for 3 monthly doses, followed by 2 mg every eight weeks or 2 mg on an as-needed (PRN) basis. *Id.* In my opinion, a POSA would have understood this disclosure to indicate that 2 mg of VEGF Trap-Eye/aflibercept showed efficacy for treating DME in prior trials.

219. Second, Elman 2010 describes the results from Phase III clinical trial of a closely related VEGF antagonist ranibizumab (*i.e.*, Lucentis ®), which was also regularly used as the control or comparison dose in the known clinical trials for aflibercept at the time. *See, e.g.* Ex. 1005, 2009 Press Release; Ex. 1009, Dixon. Notably, after the required fourth initial monthly dose was given according to the Elman 2010 protocol, clinicians thereafter performed an assessment every month (through week 52) in conjunction with a real-time data entry system referred to as a “Retreatment Algorithm,” and categorized patients as “success,” “improvement,” “no improvement,” or “failure.” Ex. 1018, Elman 2010, 1066, Appendix 2. The designation “depend[ed] mostly on visual acuity and OCT [“optical coherence

tomography”] measurements.” *Id.* Based on that assessment, clinicians were guided as to whether to provide another injection that month or not.

220. In the deferred laser group, this approach resulted in an injection at least 78% of patients receiving a fifth initial monthly doses (i.e. an injection at the fifth visit). *Id.* at 1067 (reporting that 22% of patients did not receive a fifth dose).

221. Given routine clinical practice, a POSA would have found it obvious to treat at least some patients with DME by administering five initial monthly loading doses, instead of three (or four or six), in view of Elman 2010. As set out in Section X.A.7., Elman 2010 describes the results from Phase III clinical. In my opinion, based on Elman 2010’s teaching, a POSA would have found obvious to use the dosing regimen under which an anti-VEGF injection is administered to DME patients every 4 weeks for the first 5 injections, followed by an injection approximately every 8 weeks or every 2 months with a reasonable expectation of success.

**(1) A POSA Would Have Been Motivated to
Combine the September 14, 2009 Press Release
with Elman 2010’s Dosing Regimen**

222. In my opinion, a POSA reviewing the 2009 Press Release would have found it natural to adopt, at least for some patients, teachings from the study of another anti-VEGF agent, ranibizumab, that five monthly loading doses were

deemed desirable for at least 78% of patients.⁸ Modifying the dosing regimen disclosed by the press release required only ensuring a greater likelihood of success in treating at least some patients by adopting a dosing regimen with a single additional dose between month 3 and 5. POSAs would have been motivated to take this step based on clinical experience and trial results that showed that without sufficient initial monthly dosing, it was more difficult to use the “less frequent” maintenance dosing to sustain “control of neovascular leakage and.... gains in visual acuity....” Ex. 1039, Heier 2011; Ex. 1038, Heier 2012.

⁸ Both aflibercept and ranibizumab were known anti-VEGF agents. Ranibizumab was regularly used as the control or comparison dose in the known clinical trials for aflibercept at the time. *See, e.g.* Ex. 1005, 2009 Press Release; Ex. 1009, Dixon. In fact, the Press Release notes throughout that aflibercept is being evaluated against ranibizumab in multiple trials, providing a POSA further motivation to look to dosing regimens using ranibizumab to treat DME. Moreover, Elman 2010 teaches the applicability of its results for ranibizumab to other anti-VEGF treatments for DME: “[r]esults from these and other studies should complement knowledge regarding the safety and efficacy of ranibizumab and other anti-VEGF drugs, alone, or in combination with laser, for the treatment of DME.” Ex. 1018.

223. A POSA would have been motivated to use additional initial monthly loading doses at least for some patients on this basis. This is particularly so given that Elman 2010 had determined that five loading monthly loading doses of ranibizumab, a related anti-VEGF agent, were desirable for at least 78% of patients according to its protocol. In fact, in my opinion, POSAs would have found the Elman 2010 teachings particularly compelling in comparison to the three initial doses suggested in the 2009 Press Release because the Elman 2010 results reflected the work of clinicians to make real world assessments of DME patients during the course of treatment, including as to improvements (or lack thereof) in their visual acuity and retinal thickness.

224. Additionally, I understand that because the claim language is directed to treating “a patient,” and not a complete population or percent thereof, that to show the obviousness of claim 25 here there is no requirement that a POSA would have been motivated to adopt five initial loading doses for all patients. Even if that were a requirement, however, based on the teaching of Elman 2010 that a fifth initial monthly loading dose was desirable for at least 78% of patients in the relevant group, Elman 2010 would have made five initial loading doses an obvious starting point for the treatment of all patients, even if, in my opinion, in routine practice a POSA would in fact adjust the regimen from there. Ex. 1018.

225. Additionally, as of 2010, POSAs recognized that (1) aflibercept and ranibizumab were closely related as the leading anti-VEGF agents/candidates for treating eye disorders, (2) aflibercept was successful in treating DME in prior clinical trials and was being evaluated under a dosing schedule requiring three initial monthly loading doses of 2 mg followed by 8-week/bi-monthly dosing, (3) the less frequent dosing schedule of ranibizumab proved superior over other traditional treatments (*e.g.*, laser treatment) for DME. *See, e.g.*, Section V; Ex. 1005; Ex. 1009.; Ex. 1018. In view of these prior art teachings, it is my understanding that a POSA would have found it obvious to apply a related prior art ranibizumab dosing schedule that was successful in treating DME, to that of the newer, but known anti-VEGF agent, aflibercept that had shown effectiveness for treating DME in prior clinical trials.

226. First, 2 mg aflibercept as a potential treatment for angiogenic eye disorders was well known by 2010. For example, the 2009 Press Release reported that 2 mg VEGF Trap-Eye/aflibercept was in Phase 3 development for the treatment of AMD and CRVO, as well as Phase 2 clinical trials for DME. Ex. 1005, 1. All of these clinical trials included assessment of 2 mg aflibercept dosing. *Id.* Specifically in the context of DME, it was well publicized to POSAs that VEGF Trap-Eye/aflibercept was being evaluated in a Phase 2 clinical trial in which VEGF Trap-Eye/aflibercept dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three

monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses was being compared to focal laser treatment, the standard of care in DME at the time. *Id.*, 1.

227. Moreover, Elman 2010 teaches the applicability of its results for ranibizumab to other anti-VEGF treatments for DME: “[r]esults from these and other studies should complement knowledge regarding the safety and efficacy of ranibizumab and other anti-VEGF drugs, alone, or in combination with laser, for the treatment of DME.” Ex. 1018, Elman 2010, 1076. Both aflibercept and ranibizumab were well known anti-VEGF agents.

228. Second, as a general matter, ranibizumab was regularly used as the control or comparison dose in the known clinical trials for aflibercept at the time. *See, e.g.* Ex. 1005, 2009 Press Release; Ex. 1009, Dixon. For instance, the 2009 Press Release reported that aflibercept is being evaluated against ranibizumab in multiple clinical trials (*e.g.*, VIEW program for AMD). Ex. 1005, 1. In my opinion, this would have further motivated a POSA to look to dosing regimens of ranibizumab to treat DME – where that dosing regimen has already proved efficacious in treating DME.

229. Moreover, the dosing regimen disclosed in Elman 2010 represented an attempt to determine the optimal dosing schedule for an anti-VEGF agent based on an assessment of patient progress made during the course of treatment. Ex. 1018.

Thus, it showed that the Elman 2010 dosing regimen was not the result of arbitrary choices, but reflected the work of clinicians who made in-field assessments of DME patients during the course of treatment so as to maintain improvements of visual acuity and retinal thickness while minimizing patient burden. In my opinion, this would have provided a compelling reason for a POSA to adopt the dosing regimen taught in Elman 2010.

230. Accordingly, in my opinion, a POSA would have been motivated to combine the 2009 Press Release's teaching regarding the effectiveness of 2 mg VEGF-Trap Eye/aflibercept for DME with the dosing regimen taught by Elman 2010. Both describe methods of treating DME with intravitreal administration of VEGF antagonists. And the state of the art at the time of the alleged invention made clear that VEGF antagonists, such as VEGF Trap-Eye (aflibercept) and ranibizumab, were effective for the treatment of DME. *See, e.g.*, Ex. 1009, Dixon; Ex. 1040, Pai 2010, 147 (VEGF Trap-eye's "single intravitreal injection has been found to be effective in patients with DME."). A POSA would have found it obvious to use 2 mg aflibercept in the same dosing schedule that had already proven effective with ranibizumab.

(2) A POSA Would Have Had a Reasonable Expectation of Success in Combining the

**September 14, 2009 Press Release with Elman
2010's Dosing Regimen**

231. It is also my opinion that a POSA would have reasonably expected success in making and using the claimed combination. The 2009 Press Release's disclosure of a Phase II trial using loading and maintenance dosing of aflibercept to treat DME would have provided a POSA with a reasonable expectation of success that such a regimen would work, including the use of maintenance dosing. The claimed combination adds one additional dose to the Phase II DME regimen with 3 monthly loading doses followed by 8-week maintenance doses disclosed in the 2009 Press Release. This additional dose would have provided a reasonable expectation of increased efficacy for a patient. Moreover, Elman 2010 already had shown the effectiveness of treating DME via ranibizumab, and aflibercept had already been compared to ranibizumab in clinical trials and shown the same or better effectiveness. *See* Ex. 1018; Ex. 1009, Dixon.

232. Moreover, the dosing regimens taught by the 2009 Press Release suggest that additional initial loading doses (such as five, rather than three) would be safe and tolerable, as one of the Phase II trials was for monthly injections only—a standard and proven safe regimen for other anti-VEGF agents. Ex. 1005, 2009 Press Release. They further suggest that secondary doses spaced eight weeks apart would be sufficient to maintain the initial gains commonly seen with anti-VEGF

agents, as another of the Phase II trials used eight week dosing throughout the trial period.

233. For instance, a POSA understood at the time that aflibercept had already been compared to ranibizumab in clinical trials and shown the same or better effectiveness. Ex. 1009, Dixon. Moreover, a POSA understood that VEGF Trap-eye/aflibercept appeared to have a “higher binding affinity” and “longer half-life” than ranibizumab, which would allow for it to be dosed in intervals at least as long as those used for ranibizumab. *See, e.g.*, Ex. 1040, Pai 2010, 147 (“The theoretical advantages of VEGF Trap-eye over ranibizumab include higher binding affinity, longer half-life,...which may translate into clinical benefits of fewer intraocular injections and longer intervals between injections.”).

234. The 2009 Press Release further supported a POSA’s understanding that less frequent dosing after initial loading doses could be effective in treating eye disorders:

Clinical Trial of Aflibercept	Dosing Regimen
Phase 2 trial for the treatment of Diabetic Macular Edema (DME). Ex. 105, 2009 Press Release, 1.	VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses as compared to focal laser treatment. Ex. 1005, 2009 Press Release, 1.
Phase 3 trials for the treatment of age-related macular degeneration (AMD). Ex. 1005, 2009 Press Release, 1.	VEGF Trap-Eye dosed at 0.5 mg and 2.0 mg monthly and 2.0 mg at an eight-week dosing interval following one

	additional 2.0 mg dose at week four. Ex. 1005, 2009 Press Release, 1.
Phase 3 trials (COPERNICUS and GALILEO) for the treatment of Central Retinal Vein Occlusion (CRVO), another cause of blindness. Ex. 2005, Press Release, 1.	VEGF Trap-Eye dosed at 2 mg or sham control monthly for six months. At the end of the initial six months, patients were dosed on a PRN (as needed) basis for another six months. All patients were eligible for rescue laser treatment. Ex. 1005, 2009 Press Release, 1.

235. Based on these clinical trials of aflibercept that were ongoing at the time, a POSA understood that (1) three or more initial monthly loading doses of aflibercept would be safe and tolerable, as all of the Phase 2 and 3 trials described in the 2009 Press Release included such initial monthly doses — a standard and proven safe regimen for anti-VEGF agents, and (2) secondary doses on a less frequent dosing interval (*e.g.*, eight-week dosing and dosing on a PRN (*pro ne rata*; as needed) basis) would be sufficient to maintain the initial efficacy commonly seen with anti-VEGF agents.

236. Consistent with this understanding, prior art also taught “[m]ethods for administering to a mammal suffering from, or at risk for, an intraocular neovascular disorder [that] include monthly dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist.” *See generally*, Ex. 1041, U.S. Patent App. Pub. US 2007/0190058A1.

237. Accordingly, a POSA would have reasonably expected to succeed in using the combination of Elman 2010 and the 2009 Press Release to treat DME. Accordingly, in my opinion, 2009 Press Release in combination with Elman 2010 renders claim 25 obvious.

10. Claims 1-5, 8-11, and 26-30 (Generic/AMD Results Claims) are Anticipated by Dixon Because the “Results Limitations” Lack Patentable Weight

238. As discussed in Section X.B.4., Dixon expressly discloses all of the limitations of the Generic/AMD Results Claims other than the “results limitations.” As noted above, the independent claims recite the amount and dosing schedule to be applied to “a patient” in need of treatment. For purposes of this section, I have been asked to assume that the “results limitations” of the ’572 patent are not entitled to patentable weight. *See also*, Ex. 1063. Thus, in my opinion, Dixon anticipates these claims for the reasons set out in Section X.B.4.

11. Claims 1-5, 8-11, 16-17, and 20-21 (Generic/DME Results Claims) are Anticipated by the 2009 Press Release Because the “Results Limitations” Lack Patentable Weight

239. The “results limitations” in the Results claims recite “wherein the patient achieves...”, “wherein the patient gains...”, or “wherein the method is as effective...” As set out in Section X.B.5., the 2009 Press Release expressly discloses all of the limitations of the Generic/DME Results Claims other than the “results limitations.” For purposes of this section, I have been asked to assume that the

“results limitations” of the ’572 patent are not entitled to patentable weight. *See also*, Ex. 1063. Thus, it is my opinion that the 2009 Press Release anticipates these claims for the reasons set out in Section X.B.5.

XI. NO SECONDARY CONSIDERATIONS

240. As noted above, I understand that certain objective factors called “secondary considerations” should also be considered when determining whether a claimed invention is non-obvious. I understand that these “secondary considerations” may be utilized to guard against a hindsight bias in consideration of the prior art, which include: (a) commercial success of a product due to the merits of the claimed invention; (b) a long-felt, but unsatisfied need for the invention; (c) failure of others to find the solution provided by the claimed invention; (d) copying of the invention by others; (e) unexpected results achieved by the invention; (f) praise of the invention by others skilled in the art; (g) lack of independent simultaneous invention within a comparatively short space of time; (h) teaching away from the invention in the prior art.

241. In my opinion, the secondary considerations here fail to show that the Challenged Claims of the ’572 patent are non-obvious.

242. ***No Unexpected Results.*** As discussed in Sections X.B.1-11, the Challenged Claims recite known methods with explicitly disclosed or obvious

results. Thus, in my opinion, there is no unexpected result for the Challenged Claims.

243. **No Long-Felt, Unmet Need.** Patent Owner cannot establish a “need” or show that any such need was “long-felt.” As discussed above, Patent Owner disclosed the claimed dosing regimen to the general public long before 2011, and any purported need for the claimed dosing regimen had been fulfilled long before the ’572 patent was filed. Indeed, POSAs had been implementing the claimed regimens well before the priority date through, for example, PRN dosing. And other successful, intravitreally injected anti-VEGF treatments existed as discussed above.

244. **No Nexus.** Patent Owner cannot establish nexus to the claimed dosing regimen of the ’572 patent because the art disclosed all of the claimed elements. Nothing about the claimed dosing regimen is a novel combination or discovery, rather, they are routine in view of the dosing regimen disclosed in the prior art.

245. For the foregoing reasons, in my opinion, there is a reasonable likelihood that the Challenged Claims are unpatentable.

XII. SUPPLEMENTATION

246. This declaration, along with the attached appendices, is based on my present assessment of material and information currently available to me.

247. I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed

to be true. Further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-identified patent.

12/14/2023

Date

/Christine M. Kay, M.D./

Christine M. Kay, M.D.