

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00739

U.S. Patent No. 10,888,601

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,888,601**

DECLARATION OF DR. EDWARD CHAUM

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TABLE OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 10,888,601
1003	Edward Chaum <i>Curriculum Vitae</i>
1004	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. <i>Am J Ophthalmol.</i> 2008;145(2):239-248. (“PIER Study”).
1005	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”)
1006	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”)
1007	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”)
1008	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”)
1009	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), https://newsroom.regeneron.com/news-releases/news-release-details/enrollment-completed-regeneron-and-bayer-healthcare-phase-3 (“September 14, 2009 Press Release”)
1010	WO 2006/047325 A1 (“Shams”)
1011	Press Release, VEGF Trap-Eye Final Phase 2 Results in Age-Related Macular Degeneration Presented at 2008 Retina Society Meeting (September 28, 2008), https://investor.regeneron.com/news-releases/news-release-details/vegf-trap-eye-final-phase-2-results-age-related-macular (“September 28, 2008 Press Release”)

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1012	Certified Prosecution History of U.S. Patent No. 10,888,601 (“‘601 patent PH”)
1013	Adis R&D Profile, Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye. Drugs R D. 2008;9(4):261-269. (“Adis”)
1014	Elman MJ, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 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”)
1015	Lucentis ® Original Approved Labeling (2006), available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_Prntlbl.pdf
1016	Eylea Label 2023 available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s075lbl.pdf
1017	Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (NCT00593450), available at: https://clinicaltrials.gov/ct2/show/NCT00593450
1018	Web Archive of the CATT Patient Eligibility Criteria (July 13, 2010), available at: https://web.archive.org/web/20100713035617/http://www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf (“CATT Study”)
1019	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”)
1020	History of Changes for Study: A Study of rhuFab V2 (Ranibizumab) in Subjects With Subfoveal Choroidal Neovascularization Secondary to

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	Age-Related Macular Degeneration (AMD) (NCT00090623), available at: https://clinicaltrials.gov/ct2/history/NCT00090623?V_1=View#StudyPageTop .
1021	ClinicalTrials.gov Background, available at: https://clinicaltrials.gov/ct2/about-site/background
1022	ClinicalTrials.gov About the Results Database, available at: https://clinicaltrials.gov/ct2/about-site/results
1023	Do DV et al., Incorporating the Latest Findings From Clinical Trials Into the Management of Diabetic Retinopathy for the Comprehensive Ophthalmologist (October 25, 2009), available at: https://aao.scientificposters.com/epsView.cfm?xvTgEJiNo9X9FYlsrbBjRKZ9ICSVGWMJbEunzn9LGZqaMHKIw4tNfg%3D%3D (“Do workshop 2009”)
1024	Pai A, El Shafei MM, Mohammed OA, Al Hashimi M., Current concepts in intravitreal drug therapy for diabetic retinopathy. Saudi J Ophthalmol. 2010 Oct;24(4):143-9. (“Pai 2010”).
1025	Final Written Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2021-00881 (Paper 94) (“338 FWD”)
1026	U.S. Dep’t Health & Human Servs., Nat’l Inst. Health, Nat’l Eye Inst., Diabetic Retinopathy: What You Should Know (Sept. 2015), https://www.nei.nih.gov/sites/default/files/healthpdfs/Diabetic_Retinopathy_What_You_Should_Know.pdf (“NIH DR”).
1027	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), https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf (“NIH AMD”)
1028	Halpern MT, Schmier JK, Covert D, Venkataraman K. Resource utilization and costs of age-related macular degeneration. Health Care Financ Rev. 2006;27(3):37-47. (“Halpern 2006”).

Exhibit	Description
1029	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”)
1030	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”)
1031	Gomez-Manzano C, Holash J, Fueyo J, et al. VEGF Trap induces antiglioma effect at different stages of disease. Neuro Oncol. 2008;10(6):940-945. (“Gomez-Manzano”)
1032	U.S. Patent No. 7,531,173 (“173 patent”)
1033	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. Proc Natl Acad Sci U S A. 2007;104(47):18363-18370. (“Rudge 2007”)
1034	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”)
1035	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”)
1036	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”)
1037	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:

Exhibit	Description
	one-year findings from the IVAN randomized trial. Ophthalmology 2012; 119(7):1399-411 (“Chakravarthy 2012”)
1038	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”)
1039	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”)
1040	Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreal injection: a comprehensive review. Retina. 2004;24(5):676-698. (“Jager”)
1041	Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (NCT00685854) (May 24, 2008), available at: https://clinicaltrials.gov/ct2/history/NCT00685854?V_1=View#StudyPageTop (“MACTEL Study”)
1042	Ranibizumab Injections to Treat Macular Telangiectasia Without New Blood Vessel Growth (NCT00685854) (November 7, 2008), available at: https://web.archive.org/web/20081107014243/https://clinicaltrials.gov/ct2/show/NCT00685854 (“MACTEL Study Wayback Machine”)
1043	Using the Wayback Machine, available at: https://help.archive.org/help/using-the-wayback-machine/
1044	U.S. Patent App. Pub. US 2007/0190058A1
1045	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”)
1046	Certified Prosecution History of U.S. Patent No. 10,130,681 B2 (“’681 patent PH”)
1047	Eylea Label 2011 available at:

Exhibit	Description
	https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf
1048	Glenn J. Jaffe, Paul Ashton, P. Andrew Pearson, Intraocular Drug Delivery (2006) (“Jaffe”).
1049	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
1050	Eylea Label May 2016, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125387s051lbl.pdf (“Eylea 2016 Label”)
1051	Scheduling Order (Dkt. 87) entered in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , NDWV-1-22-cv-00061
1052	September 28, 2022 Status Conference Transcript entered in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , NDWV-1-22-cv-00061
1053	Institution Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01226 (Paper 22) (“’601 ID”)
1054	Institution Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01225 (Paper 21) (“’681 ID”)
1055	Do DV et al., The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. <i>Ophthalmology</i> . 2011 Sep;118(9):1819-26, available at: https://www.aaojournal.org/article/S0161-6420(11)00177-1/fulltext (“Do 2011 AAO Website”)
1056	U.S. Patent No. 9,254,338 (“’338 patent”)
1057	WO 2012/097019A1 (“Yancopoulos PCT Application”)

I. INTRODUCTION

1. I have been retained by the law firm Quinn Emanuel Urquhart & Sullivan on behalf of Samsung Bioepis Co., Ltd., (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. 10,888,601 (“the ’601 Patent”) (Ex. 1001) and the scientific and technical knowledge regarding the subject matter of the ’601 Patent before and for a period following the earliest priority date of the application that led to the ’601 Patent.

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 over the past 30 years. I am being compensated for my services as an expert at my standard consulting rate of \$1500 per hour. 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 30 years of experience in the research, diagnosis, treatment, and analysis of vitreoretinal eye disorders. I received a Bachelor of Arts degree in Natural Sciences from Johns Hopkins University in 1979. I obtained my Ph.D. in Cell Biology and Genetics from Cornell Graduate School of Medical Sciences in 1986 and my M.D. from Cornell University Medical College in 1987. I completed a pediatrics residency at Massachusetts General Hospital and an ophthalmology residency at Boston University Hospital. After my residency, I completed a Retina Fellowship at Massachusetts Eye & Ear Infirmary.

6. From 1994 to 2000, I held the position of Assistant Professor of Ophthalmology at the University of Massachusetts Medical Center and served as the Interim Chief of Division of Ophthalmology between 1998 and 2000. From 2000 to 2018, I was the Plough Foundation Professor of Retinal Diseases at the University of Tennessee Health Science Center, College of Medicine. I joined faculty at the University of Tennessee Health Science Center, College of Medicine in 2000. I held the position of Assistant Professor of Ophthalmology and Pediatrics between 2000 and 2001, and Associate Professor of Ophthalmology (with tenure) between 2001 and 2006. I became full professor of Ophthalmology in 2006 and Pediatrics in 2007.

Between 2014 and 2018, I was the Director of Research at the Hamilton Eye Institute at the University of Tennessee Health Science Center.

7. I joined faculty at the Vanderbilt University Medical Center in 2018, and since 2018, I have been the Margy Ann and J. Donald M. Gass Chair and Professor of Ophthalmology & Visual Sciences. I hold joint appointments in the Department of Pathology, Immunology and Microbiology and the Department of Biomedical Engineering.

8. In my current and prior positions, I have been involved in the teaching and training of medical students, fellows, and residents in the area of ophthalmological surgical techniques, specifically, injection protocols for the administration of therapeutics for the treatment of age-related macular degeneration (AMD) and other vitreoretinal eye disorders. Further, since 2018, I began my current appointment as ophthalmologist the Vanderbilt University Medical Center.

9. I received numerous awards throughout my career. In 1998, I was awarded Research Career Award (K08) from the National Eye Institute, NIH. Between 2006 and 2013, I was elected to Best Doctors in America®. In 2009, I was awarded Senior Scientist Award from Research to Prevent Blindness. In 2013, I was awarded American Telemedicine Association Innovation Award for Hubble Telemedical, Inc. and B. Otto Wheelley Award for Excellence in Technology Transfer from the University of Tennessee. I have served as an editor, co-editor, or

editorial reviewer on the editorial board of several publications, including PLoS One, American Journal of Ophthalmology, Archives of Ophthalmology, Autophagy, British Journal of Ophthalmology, British Journal of Pharmacology, Experimental Eye Research, Investigative Ophthalmology and Visual Science, Journal of Cellular Biochemistry, Journal of Cellular Physiology, Journal of Gene Medicine, Journal of Pharmacy and Pharmacology, Lipids, Molecular Vision, Ophthalmology, Pan American Journal of Public Health, PLoS ONE, Retina, Survey of Ophthalmology, IEEE Transactions in Medical Imaging, IEEE Computers in Biology and Medicine, SPIE, and others.

10. I was and/or currently am a member in several Professional and Academic Societies, including American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology, Alpha Omega Alpha Honor Medical Society, Retina Society, Macular Society, American Telemedicine Association, Research to Prevent Blindness, and Fight for Sight, among others.

11. I have authored or co-authored over two hundred and fifty (250) publications, including book chapters, peer-reviewed scientific papers, abstracts, and other published works. These publications pertain to age-related macular degeneration, diabetic retinopathy (DR), and/or diabetic macular edema (DME), among other disorders of the eye.

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, as well as uveitis. 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 30 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, Chaum CV.

III. INFORMATION RELIED UPON

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 '601 Patent, the prosecution history of the '601 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. 1025, '338 FWD. I understand the '338 and '601 Patents

are in the same patent family and share the same specification. I have formed an opinion regarding the '601 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 ("Mylan IPR"). I understand the Mylan IPR was instituted on January 11, 2023. Ex. 1053, '601 ID. I have formed an opinion regarding the '601 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 '601 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 ’601 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. 1025, '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. 1025, '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 '601 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 '601 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 '601 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. 1026, 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. 1026, 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. 1027, 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. 1008, 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. 1027, 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. 1009, Regeneron September 14, 2009 Press Release 2; Ex. 1027, 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. 1028, Halpern 2006 37; Ex. 1008, Dixon, 1. It is estimated to be responsible for approximately 25% of patients with severe vision loss (defined as <20/200 visual acuity).

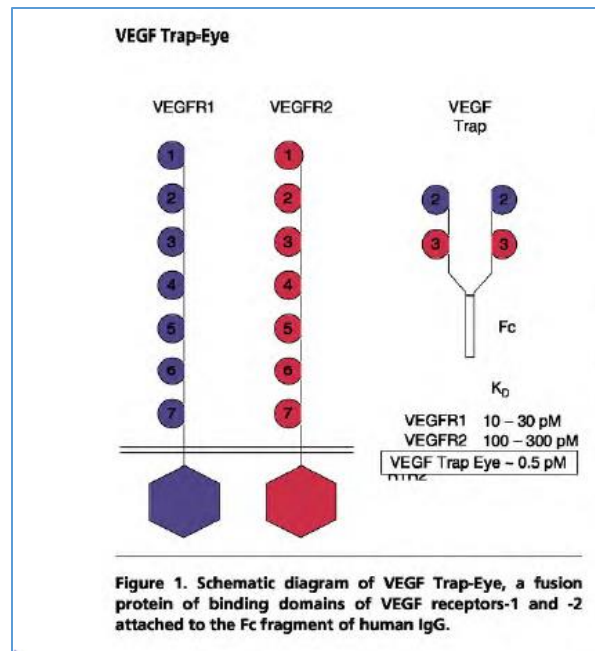
48. Wet AMD is less common but often more serious than dry AMD. The hallmark of wet AMD is the growth of irregular blood vessels under the retina. *See*, Ex. 1009, Regeneron September 14, 2009, 1-2; Ex. 1027, NIH AMD, 7-8. The leakage of fluid and blood from these vessels leads to exudation and hemorrhage. *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. 1008, 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 (PlGF).” Ex. 1009, Regeneron September 14, 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. 1029, 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. 1030, 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. 1008, 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. 1031, 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. 1013, 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-Fc Δ C1(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. 1032, ’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. 1033, 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. 1008, Dixon, 1577; Ex. 1034, 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* Exs. 1035, Brown 2009; Ex. 1036, Martin 2012; Ex. 1005, Heier 2011; Ex. 1037, Chakravarthy 2012; Ex. 1038, 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. 1008, Dixon, 1576. Results demonstrated comparable effects on BCVA due to aflibercept's longer therapy window than ranibizumab. Ex. 1005, Heier 2011; Ex. 1007, 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. 1034, 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. 1008, Dixon, 1577 ("Each injection subjects

patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis.”); Ex. 1039, 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. 1007, 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. 1039, 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. 1039, Heimann 2007, 67, 76; Ex. 1040, 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 '601 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. 1046, '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. 1039, 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. 1040, 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. 1039, 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. 1040, 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.4 and B.7 below.

VI. BACKGROUND OF THE '601 PATENT

A. General Description

70. I understand that the '601 patent is entitled "Using a VEGF Antagonist to Treat Angiogenic Eye Disorders." The '601 patent issued on January 12, 2021. The '601 patent is terminally disclaimed over U.S. Patent Nos. 9,254,338 ("'338 patent"), 9,669,069 ("'069 patent"), and 10,130,681 ("'681 patent"), as well as U.S. Patent No. 10,828,345. I understand that it will expire on January 11, 2032. The '601 patent names as its sole inventor, George D. Yancopoulos.

71. I understand that the '601 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, Col. 1:30-56. 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 2:2-7.

73. I understand that Examples 1-6 of the '601 patent describe the 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. 7-17. I note that Example 7 of the '601 patent describes additional dosing regimens, but does not contain any test results. *Id.*

74. I do not see any specific disclosure in the specification that describes the dosing regimen recited in the Challenged Claims. I only see that Example 7 of the specification discusses serially administering injections from three to eight initial loading doses, followed by different types of maintenance dosing. Ex. 1001, 15:36-17:3. The '601 patent does not report any results for these regimens, and the specification only explains that “[a]ny of the foregoing administration regimens may be used for the treatment of....” a host of angiogenic eye disorders, including AMD, RVO, CRVO, BRVO, DME, and CNV.

B. Prosecution History

75. I understand that the '601 patent issued from U.S. Application No. 16/397,267 (“the '267 application”), filed on April 29, 2019. Below, I describe my understanding of the prosecution history of the '601 patent.

76. On May 12, 2020, 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 claims 1-26 of the '338 patent; claims 1-12 of the '069 patent; claims 1-12 of the '681 patent; and claims 32-42 of co-pending U.S. Application No. 16/159,282. Ex. 1012. The examiner stated that while the specifically claimed dosing regimens were not disclosed, optimizing dosages and dosage schedules was routine experimentation. *Id.*

77. In a response dated October 21, 2020, the applicants also submitted terminal disclaimers to all four of the reference patents. *Id.* The claims of all four of these reference patents do not explicitly recite five loading doses for DR/DME, though they do recite “one or more” loading doses. *Id.* Petitioner did not argue that providing five loading doses for treating DR or DME specifically was unexpected or otherwise rendered the claims patentable. *Id.*

78. On November 12, 2020, the Examiner issued a notice of allowance for claims 21-50 and 52-68 (renumbered as claims 1-2, 7-8, 3-6, 10-16, 18-19, 21-22, 20, 23-24, 26-32, 34-35, 37-43, 46-47, 44-45, 9, 17, 25, 33 and 36, respectively). *Id.*

The examiner withdrew the obviousness-type double patenting rejection in view of the terminal disclaimers. *Id.*

VII. CHALLENGED CLAIMS

79. I understand that independent claims 10, 18, and 26 at issue here are directed to methods for treating DME, DR, and DR in a patient DME, respectively. Each independent claim further recites “intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.”

80. Dependent claims 11-17, 19-25, and 27-33 recite additional limitations concerning the methods of treatment, including the disease treated, visual acuity results, exclusion criteria, and dose amount.

81. Claims 46 and 47 depend from claim 34. Claim 34 recites the same dosing regimen as independent claims 10, 18, and 26 but does not specify the number of initial loading doses is five. Claims 46 and 47 specify that the angiogenic eye disorder is diabetic retinopathy and diabetic macular edema, respectively.

VIII. CLAIM CONSTRUCTION

82. Given the similarities between the claims in the '601 and '338 patents and based on my review of the '338 FWD, I agree with the constructions adopted by the Board in the '338 IPR and Mylan 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..." / "an effective amount" / "effective"

83. I have analyzed the '601 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.

84. I understand that the '601 patent specification defines "therapeutically effective amount" as "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." Ex. 1001, '601 patent at 6:58-65. I note that this definition similarly does not require any particular level of efficacy, and "an effective amount" in the body of the challenged independent claims (claims 10, 18, 26) as well as "effective" in claim 34 (from which claims 46 and 47 depend) should

be construed consistent with the definition of “therapeutically effective amount” in the specification.

85. 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.

86. I also understand that the Board indicated its analysis of the preamble of the ’338 patent claims is equally applicable to the preamble of the ’601 patent claims in the Mylan IPR. I agree with that understanding, and the same reasoning applies to the term “effective amount.”

87. I note that the claim language differs from the claims construed in the ’338 FWD only insofar as the body of the ’601 claims recite “administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.” The ’338 patent claims do not recite any “effective” or “therapeutically effective” amount. But the ’601 Challenged Claims specify the exact amount and dosing regimen that is “effective”—“an effective amount of

aflibercept which is...” 2 mg of aflibercept administered via five initial injections spaced four weeks apart, followed thereafter by injections every eight weeks.

88. Any requirement of efficacy in “treating” or “effective amount” is thus met by simply administering the treatment to a patient as recited in order to treat them for DR or DME, given that the claim directly defines what an “effective amount” is. In other words, administration of aflibercept to a patient for the purpose of treating them using the recited dosing regimen is sufficient.

89. This is consistent with the specification. The specification discusses the “Amount of VEGF Antagonist Administered” (*see* Ex. 1001, 6:29–7:14) 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.

90. This is also consistent with the dependent claims. Each challenged independent claim has two dependent claims that alternatively specify that “the patient **loses** less than 15 letters of Best Corrected Visual Acuity (BCVA) score” (3 lines on a standard Snellen eye chart) and “the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA).” Other dependent claims further specify that the BVCA is measured “according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” Given that both of these outcomes—a loss of 15 letters and a gain of 15 letters—are within the claimed range for “treating” and “effective amount,” a POSA would have understood that no particular level of efficacy is required.

91. Instead, consistent with the claim language and specification, the “method of treating” and “effective amount” limitations require only that the recited method be administered, and that it have the purpose of treating a patient to achieve an improvement or beneficial effect—not that it achieves a particular level of efficacy.

B. “Wherein the patient [loses less than/gains at least] 15 letters of Best Corrected Visual Acuity (BCVA) score” (Claims 13, 15, 22, 23, 29, and 31)

92. The independent claims recite “comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks

or once every 2 months.” The “wherein the patient [loses less than/gains at least]” 15 letters language appears in the dependent claims 13, 15, 22, 23, 29, and 31.

93. It is my understanding that a POSA would have considered that these dependent claims recite the intended results of administering aflibercept according to the claimed method. In other words, so long as the “effective amount” recited in the independent claim is given as recited, the patient will achieve the claimed result of losing less than, or gaining, 15 letters of BVCA score.

94. I note that from the viewpoint of a POSA, these limitations do not change or alter what the claims recite in terms of treating a patient.

95. I have been asked to assume that these claims are not entitled to patentable weight, unless noted otherwise below.

C. “The method of [claims 15/23/32] wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score” (Claims 14, 15, 20, 24, 30, and 32)

96. Claims 14, 15, 20, 24, 30, and 32 recite “wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.” A POSA would not consider these claims to have any functional relationship to the method claimed. ETDRS letter score is a merely specific way of calculating visual acuity. ETDRS charts present a series of five letters of equal difficulty on each row, with 14 total lines (70 letters). The score can be calculated when the patient correctly reads 20 or more letters at 4 meters. In that

case, the visual acuity letter score is equal to the total number of letters read correctly at 4 meters plus 30. If the patient correctly reads less than 20 letters at 4 meters, the visual acuity letter score is equal to the total number of letters read correctly at 4 meters, plus the total number of letters in the first six lines read correctly at 1 meter.

97. These claims merely provide a POSA with information about how the BVCA lost or gained by a patient is calculated. They do not provide a step in the method claimed to be taken.

98. I have been asked to assume that these claims are not entitled to patentable weight, unless noted otherwise below.

D. “Exclusion Criteria”

99. 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 the Challenged Claims, are entitled to no patentable weight, and thus should not be treated as claim limitations. Ex. 1053, '601 ID, 12-15; *see also* Ex. 1054, '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. 1053, ’601 ID, 14; *see also* Ex. 1054, ’681 ID, 19.

100. I have been asked to assume that these claims are not entitled to patentable weight, unless noted otherwise below.

101. 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”)

102. As I discuss further below, it would have 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

103. 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.

104. 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.

105. 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.

106. 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. Claims 10-33 of the '601 Patent Have an Earliest Effective Filing Date of July 12, 2013 at Best

107. As an initial matter, I note that I further address the priority date of claims 13-16, 20, 22-24, and 29-32 below in Section X.B.6.a, though as with the remainder of the claims, they are not entitled to any priority date before, at least, July 12, 2013.

108. I understand that each of claims 10-33 requires the treatment of diabetic macular edema or diabetic retinopathy through treatment with “an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks [or 2 months].” I understand that such a dosing regimen was not described in the specification of any application to which the '601 patent claims priority until July 12, 2013.

109. 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. 1056, ’338 patent.

110. 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.1056, 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. 4:13-22.

111. 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, DR, or DME in a patient with DR), nor any indication of what an “effective” combination of those variables would be for the treatment of DME or DR. *See* Ex. 1057. 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.*

112. 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 32 different “therapeutically effective” dosing amounts and 17 different disorders. *See* Ex. 1057; *see also* Ex. 1001 at Col. 3:58-67; col. 6:54-7:19. That is a total of 304,640 possible combinations.

113. 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 in the claims out of these 304,640 combinations. And, because the specification recites “etc.” and “or more” for these variables, the possibilities are effectively infinite.

114. 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.

115. 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

116. I understand the September 14, 2009 Press Release was published on September 14, 2009. Ex. 1009. 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 and acknowledged by Applicants as prior art, but never substantively addressed by the Examiner.

117. The September 14, 2009 Press Release discusses VEGF Trap-Eye, also known as aflibercept. *See, e.g.*, Ex. 1013, Adis; Ex. 1008, 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. 1009, 1. It teaches that the trial will involve three different dosing regimens: “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. Shams 2006

118. 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. 1010. Shams published in 2006. *Id.*

119. 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. 1010, 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.

120. 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]. 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.” Ex. 1010, Shams, 22-23.

3. Elman 2010

121. 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.

122. 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. 1006, 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.

123. 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. 1006, Elman 2010, 1066, 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.

124. 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. 1006, 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).

125. 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. 1006, 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.

126. 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.

127. 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. 1006 at 1074.

128. 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. 1006 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.*

4. CATT and PIER Studies

129. 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. 1018)), the MACTEL Phase 2 trial (a pilot study for Lucentis (ranibizumab)) (“MACTEL Study” and “MACTEL Study Wayback Machine” (Ex. 1041-42)), and the PIER Study evaluating the efficacy and safety of ranibizumab (“PIER Study” (Ex. 1004)).

130. 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) <i>active intraocular inflammation</i> ” – i.e. current inflammation within the eye	“<i>Active</i> or recent (within 4 weeks) <i>intraocular inflammation</i> (grade trace or below) in the study eye.” Ex.1018, CATT Study, 6-7. “<i>Active intraocular inflammation</i> (grade trace or above) in the study eye.” Ex.1004, PIER Study, 248.e3.
“(2) <i>active ocular or periocular infection</i> ” – i.e. a current infection anywhere on/in the eye (ocular) or surrounding it within its orbit (periocular)	“<i>Active</i> infectious conjunctivitis, keratitis, scleritis, or endophthalmitis <i>in either eye</i>.” Ex.1018, 6-7. “<i>Infectious</i> conjunctivitis, keratitis, scleritis, or endophthalmitis <i>in either eye</i>.” Ex.1004, 248.e3.

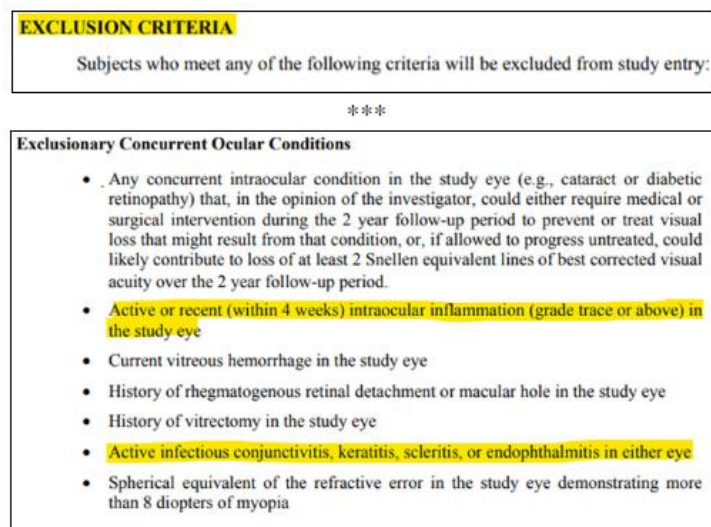
a) The CATT Study Exclusion Criteria

131. 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. 1017, NCT00593450, ClinicalTrials.gov (available at <https://clinicaltrials.gov/ct2/show/NCT00593450>). I understand that the University of Pennsylvania was the sponsor of the study. Ex. 1018, CATT Study.

132. I understand that Exhibit 1031 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. 1018, CATT Study; *see also* Ex. 1043, Using the Wayback Machine. I understand that Exhibit 1018 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.

133. 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”:



Ex. 1018, CATT Study, 2.

b) The PIER Study

134. 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. 1019, 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.

135. 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.

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

5. Prior Art Knowledge Regarding the Relationship Between DR/DME

137. I understand that three independent claims are challenged here: claims 10, 18, and 26. They recite the same dosing regimen for treating DME, DR, or DR in a patient with DME.

138. Each claim recites intravitreally administering “an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg once every 8 weeks or once every 2 months.” The prior art confirming the obviousness of claim 10 directed to treating DME is equally applicable to claim 18 and 26 directed to DR or DR in a patient with DME.¹ This is because DR and DME are a set of related conditions. It was well known by 2010 that DME is a manifestation of DR, and the effectiveness of a treatment for DME is directly linked to its effectiveness for DR. For example, numerous prior art publications relate DR with DME and vice versa, including Elman 2010:

“Macular edema is a frequent manifestation of diabetic retinopathy and an important cause of impaired vision in individuals with diabetes.” Ex. 1006, Elman 2010 at 1064.

“The rationale for anti-VEGF therapy for DME is based on the observation that VEGF levels are increased in the retina and vitreous of eyes with diabetic retinopathy.” *Id.*

“Diabetic macular edema (DME) is the commonest cause of visual loss in diabetic retinopathy.” Ex. 1023, Do Workshop 2009 at 48.

“The two main causes of visual loss/impairment in patients with diabetic retinopathy are: proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME).” Ex. 1024, Pai 2010 at 144.

¹ Similarly, the prior art for claim 46 is equally applicable to claim 47 as discussed below.

139. Moreover, I note that the specification for the '601 patent confirms this understanding. For example, the specification states “DME is the most prevalent cause of moderate vision loss in patients with diabetes and is a common complication of diabetic retinopathy, a disease affecting the blood vessels of the retina. Ex. 1001, '601 patent at 1:38-41.

140. Claims 10, 18, and 26 are identical in all other respects. Therefore, in view of a POSA's understanding at the time of the patent that the treatment for DME would likewise work for DR and vice versa, claim 18 and 26 are obvious for the same reasons as claim 10 as shown below.

B. Analysis

1. The 2009 Press Release Anticipates and/or Renders Obvious Dependent Claims 46 and 47

141. I understand that claims 46 and 47 specify that the angiogenic eye disorder is diabetic retinopathy and diabetic macular edema, respectively. Claims 46 and 47 depend from claim 34. Claim 34 recites an “effective” dosing regimen for treating a patient with an angiogenic eye disorder in which a single initial dose of aflibercept is given, followed by one or more secondary doses administered every 4 weeks, followed by one or more tertiary doses administered every 8 weeks.

142. As noted above, the 2009 Press Release reports 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. 1009, 1. As noted in Section V.D., I understand that VEGF Trap-Eye was another name for aflibercept (and that the recited structure was known).² Aflibercept was already known to be effective for DME (Ex. 1008, Dixon), and a POSA would have understood from the fact a clinical trial was being undertaken (including comparing to focal laser treatment) that the dosing regimen described in the 2009 Press Release was intended for treatment of DR/DME and would be effective. Thus, in my opinion, the 2009 Press Release’s discussion of the Phase 2 trial for DME anticipates the DME dosing regimen of claim 47, in which an initial loading dose of aflibercept is administered, followed by secondary doses one month apart, followed by maintenance doses at 8-week intervals. Ex. 1009, 2.

143. As I noted in Section X.A.5., DME was a known symptom of DR, and POSAs understood that treating DME was a way to address the underlying DR. In other words, the DME dosing regimen disclosed in the 2009 Press Release would have necessarily been for the purpose of effectively treating DR. Thus, in my opinion, the 2009 Press Release’s disclosure of the DME dosing regimen in claim 47 inherently anticipates the DR dosing regimen in claim 46.

² I note that aflibercept is described in the claim by the structural components of the protein, which were disclosed in the art as discussed in Section V.D.

144. I also believe that a POSA would have found it obvious to use the DME dosing regimen disclosed in the 2009 Press Release for treating DR, to the extent not disclosed. In my opinion, a POSA would have been motivated to review the 2009 Press Release because it understood that DME is a manifestation of DR, and the effectiveness of a treatment for DME is directly linked to its effectiveness for DR. *See* Section X.A.5. Thus, based on the 2009 Press Release’s discussion of the ongoing clinical trials for DME and AMD utilizing the same dosing regimen, a POSA would have had a reasonable expectation that administering aflibercept according to the disclosed DME dosing regimen would also work for DR and could be administered for that purpose.

145. Accordingly, in my opinion, claims 46 and 47 are anticipated and/or rendered obvious by the 2009 Press Release.

2. Claims 10, 18, and 26 Are Rendered Obvious by the September 14, 2009 Press Release Either Alone Or In View Of Shams

146. In my opinion, the Regeneron September 14, 2009 Press Release either alone or in view of Shams renders claims 10, 18, and 26 obvious.

147. First, the Regeneron September 14, 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. 1009. 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.*

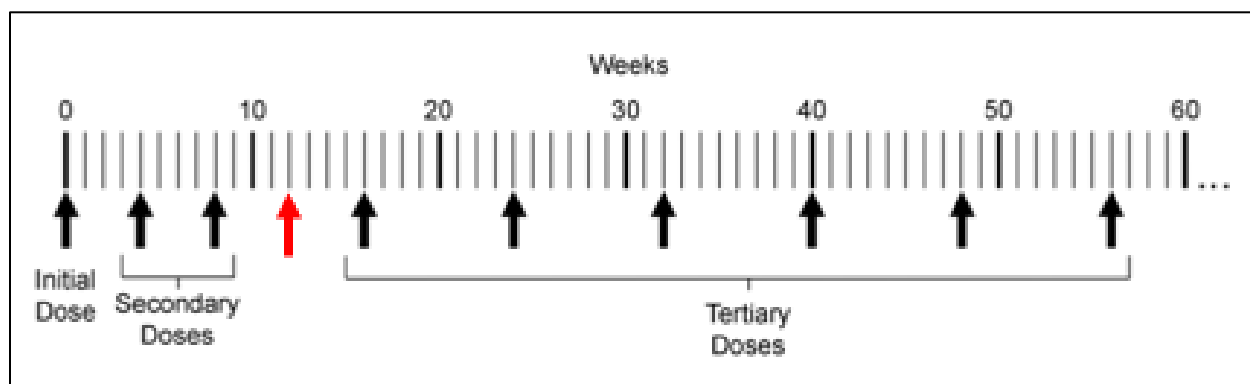
148. As discussed in Section V.E, the primary problems associated with monthly injections were patient burden and injection complications. Thus, a POSA reading the Regeneron September 14, 2009 Press Release would have understood that Regeneron was pursuing multiple different dosing regimens with 2 mg 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.

149. 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. 1009.

150. 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.

151. 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. 1006, Elman 2010.³ This is effectively what Elman 2010 studied.

152. 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 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 ’601 patent’s sole figure, which discloses a regimen involving three initial doses as disclosed in the press release:



³ As noted below, in Elman 2010, at least 78% of patients received a fifth initial loading dose in the ranibizumab + deferred laser group. Ex. 1006, 1067.

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

153. 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.

154. I find the disclosures of the '601 patent consistent with this understanding. The '601 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 '601 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 '601 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, 17:16-27. This mirrors exactly how a POSA would have evaluated the appropriate dosing regimen for an individual DR/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 DR/DME before moving to maintenance dosing for individual patients, including the use of five loading doses.

155. 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.1010, 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 (emphasis added).

156. 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.

157. 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. 1006, Elman 2010, at 1064-65. Phase 1 testing of a single 4 mg injection of aflibercept for DME, showed significant improvement—patient’s BVCA increased by 9 letters with a decrease of 79 μm 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. 1008, 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.

158. Furthermore, the clinical trials taught by the Regeneron September 14, 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 Regeneron September 14, 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 Regeneron September 14, 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. 1009.

3. The Regeneron September 14, 2009 Press Release in Combination with Elman 2010 Renders Obvious Claims 10, 18, and 26

159. In my opinion, the recited dosing regimen is obvious over the Regeneron September 14, 2009 Press Release in combination with Elman 2010.

160. First, the Regeneron September 14, 2009 Press Release teaches the use of 2mg of VEGF Trap-Eye to treat DME (and accordingly, the underlying condition DR, as explained above). Ex. 1009, 1. Specifically, the Regeneron September 14, 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.

161. 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. 1009, September 14, 2009 Press Release; Ex. 1008, 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. 1006, 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.

162. 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).

163. Given routine clinical practice, a POSA would have found it obvious to treat at least some patients with DR/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.3, 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.

a) A POSA Would Have Been Motivated to Combine the September 14, 2009 Press Release with Elman 2010's Dosing Regimen

164. In my opinion, a POSA reviewing the September 14, 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.⁴ Modifying the dosing regimen disclosed by the press release required only ensuring a greater likelihood of

⁴ 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. 1009, September 14, 2009 Press Release; Ex. 1008, Dixon. In fact, the September 14, 2009 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.”

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. 1005, Heier 2011; Ex. 1007, Heier 2012.

165. 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.

166. 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 the Challenged Claims 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. 1006.

167. 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. 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.

168. First, 2 mg aflibercept as a potential treatment for angiogenic eye disorders was well known by 2010. For example, the Regeneron September 14, 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. 1009, 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.

169. 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. 1006, Elman 2010, 1076. Both aflibercept and ranibizumab were well known anti-VEGF agents.

170. 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. 1009, September 14, 2009 Press Release; Ex. 1008, Dixon. For instance, the Regeneron September 14, 2009 Press Release reported that aflibercept is being evaluated against ranibizumab in multiple clinical trials (*e.g.*, VIEW program for AMD). Ex. 1009, 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.

171. 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. 1006. 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.

172. Accordingly, in my opinion, a POSA would have been motivated to combine the Regeneron 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. 1008, Dixon; Ex. 1024, 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.

b) A POSA Would Have Had a Reasonable Expectation of Success in Combining the September 14, 2009 Press Release with Elman 2010's Dosing Regimen

173. It is also my opinion that a POSA would have reasonably expected success in making and using the claimed combination. As set out above in Section X.A.1, 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 DME regimen with 3 monthly loading doses followed by 8-week maintenance doses disclosed in the September 14, 2009 Press Release. The additional dose of a single dose would have provided an additional visual acuity gain 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. 1006; Ex. 1008, Dixon.

174. Moreover, the dosing regimens taught by the September 14, 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. 1009,

September 14, 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.

175. 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. 1008, 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. 1024, 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.”).

176. The Regeneron September 14, 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. 1009, Regeneron September 14, 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.

	1009, Regeneron September 14, 2009 Press Release, 1.
Phase 3 trials for the treatment of age-related macular degeneration (AMD). Ex. 1009, Regeneron September 14, 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. 1009, Regeneron September 14, 2009 Press Release, 1.
Phase 3 trials (COPERNICUS and GALILEO) for the treatment of Central Retinal Vein Occlusion (CRVO), another cause of blindness. Ex. 1009, Regeneron September 14, 2009 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. 1009, Regeneron September 14, 2009 Press Release, 1.

177. 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 Regeneron September 18, 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.

178. 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. 1044, U.S. Patent App. Pub. US 2007/0190058A1.

179. Accordingly, a POSA would have reasonably expected to succeed in using the combination of Elman 2010 and the Regeneron September 14, 2009 Press Release to treat DME.

4. The Dependent Claims Are Rendered Obvious by the September 14, 2009 Press Release Alone or in View of Elman 2010

a) Claims 11/19/27: “The method of [claims 10/18/26] wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.”

180. Claims 11, 19, and 27 recite “wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.” In my opinion, a POSA would have understood that 4 weeks consist of 28 days and that the term is used interchangeably with “monthly.” *See also, e.g.*, Ex. 1006, Elman 2010 at 1077.e1 (describing injections four weeks apart as monthly – “At the 16 and 20 week study visits, sham or study drug was required monthly unless ‘success’ criteria...was met.”). It was common sense then and now that 4 weeks comprise 28 days and are approximately one month. None of the prior art references I reviewed here use these terms any differently.

b) Claims 12/21/28: “The method of [claims 10/18/26] further comprising, after 20 weeks, administering, via

intravitreal injection, 2 mg of aflibercept once every 4 weeks.”

181. Claims 12, 21, and 28 recite “further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.” Claims 10, 18, and 26 from which claims 12, 21, and 28 respectively depend are directed to administering aflibercept “every 4 weeks for the first 5 injections followed by once every 8 weeks or once every 2 months.” In my opinion, the requirement of dosing every 4 weeks for the first five injections followed by dosing every 8 weeks recited by claims 10, 18, and 26 is facially inconsistent with dosing every 4 weeks “after 20 weeks” recited by claims 12, 21, and 28.

182. To the extent Patent Owner argues that claims 12, 21, and 28 should be read as requiring dosing every 4 weeks, the Regeneron September 14 2009 Press Release discloses such dosing as one arm of the VEGF Trap-Eye Phase 2 clinical trial for DME that renders such claims obvious. *See* Ex. 1009, Regeneron September 14, 2009, 1.

183. To the extent Patent Owner argues that claims 12, 21, and 28 should be read as dosing every 4 weeks through week 16, followed by 8 week intervals between doses, and then dosing every 4 weeks starting at a later point (“after 20 weeks”), such a protocol would be the result of routine experimentation, particularly in patients that show regression. *See, e.g.* Ex.1006, Elman 2010.

184. Therefore, in my opinion, claims 12, 21, and 28 are, under any interpretation of those claims, rendered obvious.

5. Claims 13-16, 20, 22-24, and 29-32 Are Rendered Obvious by the September 14, 2009 Press Release, Either Alone and in Combination with Elman 2010, and Further in View of Do 2011

185. I understand that claims 13-16, 20, 22-24, and 29-32 recite that the patient either loses less than or gains at least 15 letters Best Corrected Visual Acuity (BCVA).

186. In my opinion, it would have been obvious to a POSA that at least some patients would achieve 15 letter gains when treated via five initial loading doses followed by 8-week maintenance dosing. Ex. 1001, cl. 1. This is because the claims do not require the dosing regimen to apply to all patients populations. Rather, the claims are directed to a “method for treating diabetic macular edema in *a* patient.”

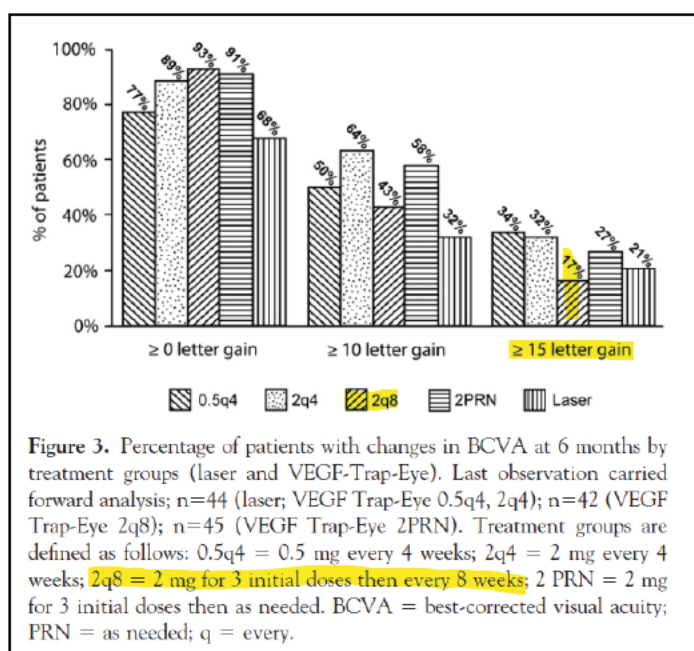
187. First, the September 14, 2009 Press Release discloses that, in the VIEW 1 study, which involved the use of three monthly loading doses followed by 8-week dosing intervals, “[m]aintenance of vision is defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS chart.” It further discloses that a secondary endpoint of that study is the “proportion of patients who gained at least 15 letters of

vision at week 52.”⁵ Regarding the Phase 2 trial for the treatment of DME, the September 14, 2009 Press Release notes that the “primary efficacy endpoint evaluation is mean improvement in visual acuity at six months”—not just maintenance.

188. A POSA would have found it obvious that the Phase 2 trial for treatment of DME, studying the same number of initial loading doses as the VIEW 1 study, would be expected to produce similar maintenance of vision and improvement for at least some patients as was expected to be produced in the VIEW 1 study. In other words, a POSA would not have found surprising or unexpected that a patient would lose no less than or gaining at least 15 letters of vision (even if others did not) in the Phase 2 trial for treatment of DME. A POSA further would have appreciated that adding additional monthly loading doses via routine adjustment to the dosing regimen disclosed in the September 14, 2009 Press Release could have only improved the number of patients losing no less than or gaining at least 15 letters of vision, not worsen the clinical outcome.

⁵ It further states that “[v]isual acuity is defined as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, a standard chart used in research to measure visual acuity.”

189. This understanding of a POSA is further confirmed by Do 2011,⁶ which was published May 5, 2011 and reports the results of the Phase 2 clinical trial disclosed by the September 14, 2009 Press Release. Ex. 1045 Do 2011 discloses that after six months of treatment via the dosing regimen described in the September 14, 2009 Press Release (“2q8” in the chart below) that 17% of patients achieved at least a 15 letter gain, as shown in the chart below:



Ex. 1045, 1822.

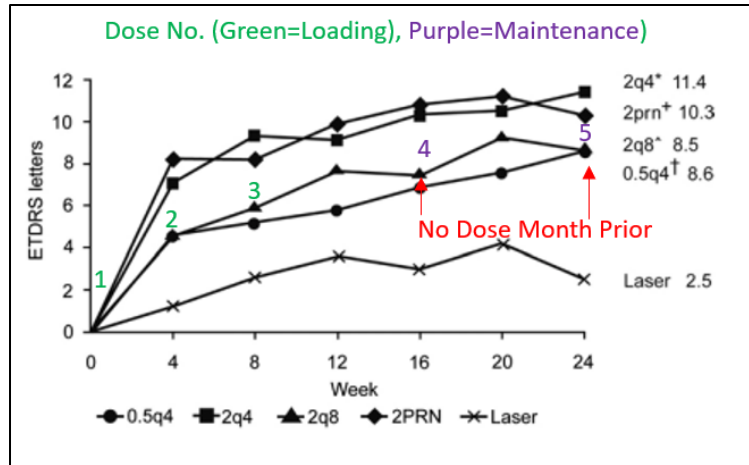
190. As shown above, 32% of patients that received monthly 2mg doses (“2q4”) achieved 15 letter gains at six months (i.e. after six total doses). A POSA

⁶ Ex. 1045, 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); see also Ex.1055, Do 2011 AAO Website.

would have found that this data further confirms that additional initial monthly loading doses, including, for instance, five initial loading doses, would further increase the expectation of achieving 15 letter gains in at least some patients. At least based on this data, there was nothing unexpected to a POSA about a patient gaining 15 letters via loading and maintenance dosing.

191. Moreover, in my opinion, additional data reported in Do 2011 further renders obvious that additional monthly loading doses would result in a treatment that achieves at least a 15 letter visual acuity gain.⁷ In particular, the below annotated figure from Do 2011 reports mean gains in visual acuity, in the group receiving three loading doses (“2q4,” indicated with the trend line that includes diamonds indicating clinical visits). The figure shows that visual acuity regressed in the month after a dose was not given, whereas visual acuity increased in the month after any dose was given for this group:

⁷ For the same reason, this data, which would be within the knowledge of a POSA at the time of the patent, further supports the obviousness of using five initial loading doses as part of routine adjustment to standard loading and maintenance dosing as set out in Section X.B.1-2.



Ex. 1045, 1822.

192. Thus, in my opinion, this in addition to the overall results data disclosed in Elman 2010 supports that a POSA knew well that administering additional monthly doses would result in a 15 letter gain in visual acuity in at least some patients.

a) Alternatively, Claims 13-16, 20, 22-24, and 29-32 Are Not Entitled to Patentable Weight and Are Inherent in Practicing the Method

193. In my opinion, claims 13-16, 20, 22-24, and 29-32 are not entitled to patentable weight for the reasons set out in Section VIII.D. Additionally, I understand that post-priority date evidence can be used to demonstrate what is necessarily present or inherent in a prior art embodiment. As set out below in Section X.B.6, in my opinion, the Eylea Label 2016 confirms that the claimed gains naturally result from practicing the recited method. Ex. 1050; *see also* Ex. 1016.

6. The 2016 Eylea Label Anticipates Claims 13-16, 20, 22-24, and 29-32

194. As discussed in Section VIII.D in my opinion, dependent claims 13-16, 20, 22-24, and 29-32 should not be construed to have patentable weight, as these claims merely recite the natural, inherent, intended result of practicing the claimed method. If Patent Owner argues they are not obvious or otherwise inherent because the results are unexpected, then my understanding is that in that case they would not be entitled to a priority date earlier than the '601 patent's April 29, 2019 filing date and are anticipated by, *inter alia*, the Eylea Label from 2016.

a) Dependent Claims 13-16, 20, 22-24, and 29-32 Are Not Entitled to a Priority Date Earlier Than April 29, 2019 if Non-Obvious

195. Claims 13-16, 20, 22-24, and 29-32 recite “wherein the patient [loses less than/gains at least]” 15 letters of Best Corrected Visual Acuity (BCVA) score (and further specify that BVCA is measured according to an ETDRS letter score). The '601 patent does not disclose any such results from practicing the claimed method. Nor does it disclose any results from a regimen including five initial loading doses. I understand that Example 7's listing of twenty different dosing regimens in the '601 patent specification is the only place where the claimed dosing regimen of five initial 2 mg doses followed by 8-week maintenance dosing is identified.

196. I understand that Example 5 of the '601 patent reports the results of the use of three initial loading doses followed by 8-week maintenance dosing to treat

DR/DME. However, I note that, unlike Do 2011, it does not report that any patient achieved a 15 letter gain. Rather, the highest reported gain in the '601 patent is 13 letters. *See* Ex. 1001 at Table 2, col. 14:9-54.

197. Thus, in my opinion, if the results of the claimed method are unexpected—and thus not inherent from practicing the claimed method or obvious over the disclosures of, *inter alia*, the September 14, 2009 Press Release and Do 2011—then the '601 patent fails to show possession of the claimed invention and is not entitled to a priority date earlier than the '601 patent's April 29, 2019 filing date.

198. In my opinion, the prior art known to a POSA discloses and teaches more than the '601 patent specification discloses regarding the claimed method and resulting efficacy. In particular, while Do 2011 teaches that both three initial loading doses and monthly loading doses produced a 15 letter gain in patients with DR/DME, there is no such disclosure or teaching in the patent. Thus, in my opinion, it is inconsistent to argue on one hand that Do 2011's teaching, let alone the teaching of the rest of the art, does not show that the claimed results were expected, while maintaining on the other that the specification sufficiently discloses the results to show possession of the claimed method and resulting efficacy.

199. Accordingly, it is my opinion that to the extent the efficacy limitations of the claimed method are construed to have patentable weight and not an inherent

result of practicing the claimed method, dependent claims 13-16, 20, 22-24, and 29-32 cannot be entitled to a priority date earlier than April 29, 2019.

b) The 2016 Eylea Label Anticipates Claims 13-16, 20, 22-24, and 29-32

200. I understand that Eylea (aflibercept) manufactured by Regeneron was approved by the FDA in 2011, and the Eylea Label was publicly available in May, 2016. Ex. 1050. I also understand that Regeneron submitted an Eylea Label revised in May 2016 as evidence in support of its patent owner response filed in IPR2021-00880 (“’069 patent IPR”).

201. The Eylea Label 2016 discloses the dosing regimen recited by the independent claims: “[t]he recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).” It also discloses efficacy data from the VIVID and VISTA Studies evaluating the claimed aflibercept dosing regimen for treating DME and DR. Specifically, Table 7 shows that ~31% (at Week 100) or ~33% (at Week 52) of patients gained at least 15 letters in BCVA upon administering aflibercept for DME according to the claimed dosing regimen. Ex. 1050, 28. Table 8 shows that 32-38% of patients achieved greater than or equal to 2-Step improvement from baseline in the ETDRS-DRSS score at Week 100 upon administering aflibercept for DR, which

include at least some with a three-step improvement and 15 letters in BCVA.⁸ Ex. 1050, 30; *see also* Ex. 1016, 31, 33. Therefore, in my opinion, claims 13-16, 20, 22-24, and 29-32 are anticipated by the Eylea 2016 Label. *See* Ex. 1050; Ex. 1016.

7. Claims 17, 25, and 33 Are Rendered Obvious by the September 14, 2009 Press Release Alone or in View of Elman 2010 and Further in View of the CATT and PIER Studies

202. Claims 17, 25, and 33 recite “[t]he method of [claims 10/18/26] wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.” The Regeneron September 14, 2009 Press Release do not recite exclusion criteria. The claimed exclusion criteria, however, were well known in the art and are disclosed therein.

203. Specifically, the CATT and PIER Studies (Exs. 1004, 1018) described above in Section X.A.4 describe the 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 ’601 patent, as is shown in Table 1 above in Section X.A.4. Applying these exclusion criteria in combination with the prior art disclosures and teaching discussed in Sections X.B.2-3 above renders the claimed method obvious.

⁸ Each step-improvement from baseline in the ETDRS-DRSS score corresponds to a gain of 5 letters in BCVA.

204. Moreover, the '601 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.

205. Finally, POSAs would have been motivated to adopt the exclusion criteria of the CATT and PIER studies and exclude patients from treatment via intravitreal injection based on active inflammation and active infections in order follow the standard of care, as set out above, as well as to solve a problem that references such as the Regeneron September 14, 2009 Press Release and Dixon address directly. Ex. 1008-1009. 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 as noted above. Ex. 1046, 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. 1015 (Lucentis label) at 1 (listing endophthalmitis and intraocular

inflammation as risks); Ex. 1004, PIER, 239-240 (same); Ex. 1009, September 14, 2009 Press Release (addressing same).

206. 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. 1004, 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. 1015, 1), as well as the 2011 Eylea label. Ex. 1047.

207. 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. 1048, 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. 1049, Steps for a Safe Intravitreal Injection Technique (2009).

208. Similarly, prior studies of anti-VEGF intravitreal injections demonstrated that a primary complication from such injections was intraocular

inflammation. Ex. 1004, 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.

XI. NO SECONDARY CONSIDERATIONS

209. 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.

210. In my opinion, the secondary considerations here fail to show that the Challenged Claims of the ’601 patent are non-obvious.

211. ***No Unexpected Results.*** As set out in Section VIII.A, the Challenged Claims do not require any particular levels of efficacy. Thus, the argument that the

less frequent regimen of the Challenged Claims produced “unexpected results” is entirely irrelevant.

212. **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 ’601 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.

213. **No Nexus.** Patent Owner cannot establish nexus to the claimed dosing regimen of the ’601 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.

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

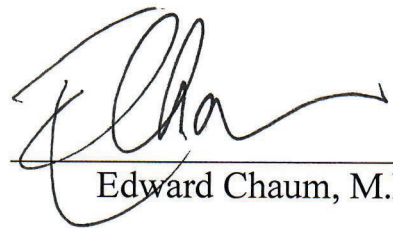
XII. SUPPLEMENTATION

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

216. 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 lie 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.

03/23/2023
Date


Edward Chaum, M.D.