

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 IPR2023-00884

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

PETITION FOR *INTER PARTES* REVIEW

OF U.S. PATENT NO. 11,253,572

RESPONSIVE DECLARATION OF DR. EDWARD CHAUM

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TABLE OF EXHIBITS

Exhibit	Description
1001	U.S. Patent No. 11,253,572
1002	Expert Declaration of Dr. Edward Chaum in Support of Petition for <i>Inter Partes</i> Review of Patent No. 11,253,572, dated April 27, 2023 (“Chaum Decl.”)
1003	Edward Chaum <i>Curriculum Vitae</i>
1004	Institution Decision in <i>Apotex Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01524. (“Apotex ’572 ID”)
1005	Press Release, “Enrollment Completed in Regeneron and Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (September 14, 2009),” available at: https://newsroom.regeneron.com/news-releases/news-release-details/enrollment-completed-regeneron-and-bayer-healthcare-phase-3 (“2009 Press Release”)
1006	Press Release, “Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME),” Exhibit 99.1 to Regeneron 8-K filed on December 20, 2010, available at: https://yahoo.brand.edgar-online.com/displayfilinginfo.aspx?FilingID=7617341-6436-23571&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6 (“December 2010 Press Release”)
1007	Press Release, “Bayer and Regeneron Report Positive Top-Line Results of Two Phase 3 Studies with VEGF Trap-Eye in Wet Age-related Macular Degeneration,” Exhibit 99.1 to Regeneron 8-K filed on November 22, 2010, available at: https://yahoo.brand.edgar-online.com/displayfilinginfo.aspx?FilingID=7572010-8611-26486&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6 (“November 2010 Press Release”)
1008	Apotex Petition for IPR filed in <i>Apotex Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01524 (Paper 1) (“Apotex Petition”)

Exhibit	Description
1009	Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. <i>Expert Opin Investig Drugs</i> . 2009;18(10):1573-1580. (“Dixon”)
1010	Major JC et al., “DA VINCI: DME and VEGF Trap-Eye: INvestigation of Clinical Impact: Phase 2 Study in Patients With Diabetic Macular Edema (DME), ARVO Annual Meeting Abstract (April 2010), Vol. 51, Issue 13, available at: https://iovs.arvojournals.org/article.aspx?articleid=2375028 (“2010 ARVO Abstract”)
1011	Final Written Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2021-00881 (Paper 94) (“338 FWD”)
1012	Institution Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01225 (Paper 21) (“681 ID”)
1013	Institution Decision in <i>Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.</i> , IPR2022-01226 (Paper 22) (“601 ID”)
1014	Certified Prosecution History of U.S. Patent No. 11,253,572 (“572 patent PH”)
1015	Adis R&D Profile, Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye. <i>Drugs R D</i> . 2008;9(4):261-269. (“Adis”)
1016	Hecht, “Ophthalmic Preparations,” Remington: The Science and Practice of Pharmacy, Volume II, 19th edition, Chapter 89 (1995). (“Hecht”)
1017	WO 2006/047325 A1 (“Shams”)
1018	Elman MJ, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. <i>Ophthalmology</i> . 2010 Jun;117(6):1064-1077.e35. (“Elman 2010”)
1019	Elman MJ, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. <i>Ophthalmology</i> . 2010 Jun;117(6):1064-1077.e35, published April 28 2010, available at https://www.aaojournal.org/article/S0161-6420(10)00243-5/fulltext (“Elman AAO Website”)

Exhibit	Description
1020	Authenticating Affidavit and the July 13, 2010 Web Archive of the CATT Patient Eligibility Criteria, available at https://web.archive.org/web/20100713035617/http://www.med.upenn.edu/cpob/studies/documents/CATTEligibilityCriteria_000.pdf , attached as Exhibit B (“CATT Study”).
1021	Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145(2):239-248. (“PIER Study”).
1022	Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (NCT00593450), available at: https://clinicaltrials.gov/ct2/show/NCT00593450 (“NCT-450”)
1023	Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol. 2008;145(2):239-248, published December 3, 2007, available at https://www.ajo.com/article/S0002-9394(07)00881-1/fulltext (“PIER AJO Website”)
1024	History of Changes for Study: A Study of rhuFab V2 (Ranibizumab) in Subjects With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD) (NCT00090623), available at: https://clinicaltrials.gov/ct2/history/NCT00090623?V_1=View#StudyPageTop . (“NCT-623”)
1025	ClinicalTrials.gov Background, available at: https://clinicaltrials.gov/ct2/about-site/background (“ClinicalTrials.gov Background”)
1026	ClinicalTrials.gov About the Results Database, available at: https://clinicaltrials.gov/ct2/about-site/results (“ClinicalTrials.gov About the Results Database”)
1027	Press Release, “Regeneron Reports Positive Phase 1 Data for the VEGF TRAP in Age-Related Macular Degeneration,” Exhibit 99(a) to Regeneron 8-K filed on May 2, 2006, available at: https://yahoo.brand.edgar-

Exhibit	Description
	online.com/displayfilinginfo.aspx?FilingID=4380124-5423-15279&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6 (“May 2006 Press Release”)
1028	Nguyen QD et al. A phase I study of intravitreal vascular endothelial growth factor trap-eye in patients with neovascular age-related macular degeneration. Ophthalmology. 2009 Nov;116(11):2141-8.e1. (“Nguyen 2009”)
1029	Press Release, “Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration” published on May 8, 2008, available at: https://investor.regeneron.com/node/10561/pdf (“May 2008 Press Release”).
1030	Do DV et al., “Results of a Phase I Study of Intravitreal VEGF Trap in Subjects With Diabetic Macular Edema: The CLEAR-IT DME Study,” ARVO Annual Meeting Abstract (May 2007), Vol. 48, Issue 3, available at: https://iovs.arvojournals.org/article.aspx?articleid=2384099 (“2007 ARVO Abstract”).
1031	Do DV et al., The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. Ophthalmology. 2011 Sep;118(9):1819-26 (published online on May 5, 2011). (“Do 2011”)
1032	Randolph and Jones, “Surfactant-Protein Interactions,” Rational Design of Stable Protein Formulations, edited by Carpenter and Manning, vol. 13, 2002 (“Randolph”)
1033	Fraser et al., Journal of Clinical Endocrinology and Metabolism, February 2005, 90(2):1114-1122 (“Fraser”)
1034	Lucentis ® Original Approved Labeling (2006), available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125156s0000_Lucentis_Prntlbl.pdf
1035	Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A. 2002;99(17):11393-11398. (“Holash”)

Exhibit	Description
1036	Rudge JS, Thurston G, Davis S, et al. VEGF trap as a novel antiangiogenic treatment currently in clinical trials for cancer and eye diseases, and VelociGene- based discovery of the next generation of angiogenesis targets. Cold Spring Harb Symp Quant Biol. 2005;70:411-418 (“Rudge 2005”)
1037	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”)
1038	Heier JS, et al., Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537-2548. (“Heier 2012”)
1039	Heier JS, et al., CLEAR-IT 2 Investigators. The 1-year results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology. 2011 Jun;118(6):1098-106. (“Heier 2011”)
1040	Pai A, El Shafei MM, Mohammed OA, Al Hashimi M., Current concepts in intravitreal drug therapy for diabetic retinopathy. Saudi J Ophthalmol. 2010 Oct;24(4):143-9. (“Pai 2010”).
1041	U.S. Patent App. Pub. US 2007/0190058A1 (“Shams US App. Pub.”)
1042	U.S. Patent No. 9,254,338 (“338 patent”)
1043	WO 2012/097019A1 (“Yancopoulos PCT Application”)
1044	U.S. Dep’t Health & Human Servs., Nat’l Inst. Health, Nat’l Eye Inst., “Diabetic Retinopathy: What You Should Know (Sept. 2015),” available at: https://www.nei.nih.gov/sites/default/files/healthpdfs/Diabetic_Retinopathy_What_You_Should_Know.pdf (“NIH DR”).
1045	U.S. Dep’t Health & Human Servs., Nat’l Inst. Health, Nat’l Eye Inst., “Age-Related Macular Degeneration: What You Should Know (Sept. 2015),” available at: https://www.nei.nih.gov/sites/default/files/healthpdfs/WYSK_AMD_English_Sept2015_PRINT.pdf (“NIH AMD”)

Exhibit	Description
1046	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”).
1047	Rudge JS, Holash J, Hylton D, et al. VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. Proc Natl Acad Sci U S A. 2007;104(47):18363-18370. (“Rudge 2007”)
1048	Li E, Donati S, Lindsley KB, Krzystolik MG, Virgili G. Treatment regimens for administration of anti-vascular endothelial growth factor agents for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2020;5(5):CD012208. (“Li 2020”)
1049	Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology. 2009;116(1):57-65.e5. (“Brown 2009”)
1050	Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al, Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012; 119(7):1388-98 (“Martin”)
1051	Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al, Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012; 119(7):1399-411 (“Chakravarthy 2012”)
1052	Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006; 355(14):1419-31 (“Rosenfeld 2006”)
1053	Heimann, H. (2007). Chapter 5 Intravitreal Injections: Techniques and Sequelae. In: Holz, F.G., Spaide, R.F. (eds) Medical Retina. Essentials in Ophthalmology. Springer, Berlin, Heidelberg. (“Heimann 2007”)

Exhibit	Description
1054	Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreal injection: a comprehensive review. <i>Retina</i> . 2004;24(5):676-698. (“Jager 2004”)
1055	Certified Prosecution History of U.S. Patent No. 10,130,681 B2 (“‘681 patent PH”)
1056	Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (NCT00685854) (May 24, 2008), available at: https://clinicaltrials.gov/ct2/history/NCT00685854?V_1=View#StudyPageTop (“MACTEL Study”)
1057	Authenticating Affidavit and the November 7, 2008 Web Archive of Ranibizumab Injections to Treat Macular Telangiectasia Without New Blood Vessel Growth (NCT00685854), available at https://web.archive.org/web/20081107014243/https://clinicaltrials.gov/ct2/show/NCT00685854 , attached as Exhibit A (“MACTEL Study Wayback Machine”)
1058	Using the Wayback Machine, available at: https://help.archive.org/help/using-the-wayback-machine/
1059	Eylea Label 2011 available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf
1060	Glenn J. Jaffe, Paul Ashton, P. Andrew Pearson, Intraocular Drug Delivery (2006) (“Jaffe”).
1061	Steps for a Safe Intravitreal Injection Technique (2009), available at: https://www.retinalphysician.com/issues/2009/july-aug/steps-for-a-safe-intravitreal-injection-technique
1062	Mylan’s Emergency Motion to Modify Scheduling Order and For Emergency Status Conference filed in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , Case No. 1:22-cv-00061-TSK, Northern District of West Virginia. (Dkt. 415) (“Mylan April 10 Motion”)
1063	April 19, 2023 Claim Construction Order entered in <i>Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.</i> , Case No. 1:22-cv-

Exhibit	Description
	00061-TSK, Northern District of West Virginia. (Dkt. 427) (“Mylan Litigation CC Order”)
1064	U.S. Patent No. 7,531,173 (“’173 patent”)
1065	U.S. Patent App. No 13/940.370 (July 12, 2013)
1066	U.S. Patent App. No 13/940.370 (July 12, 2013)
1067	Declaration of Zachariah Summers in Support of Motion for Admission <i>Pro Hac Vice</i>
1068	Declaration of Elliot Choi in Support of Motion for Admission <i>Pro Hac Vice</i>
1069	Email Correspondence Between Petitioner Samsung Bioepis and Third Party Mylan Pharmaceuticals, Inc. Regarding Discovery
1070	Email Correspondence Between Petitioner Samsung Bioepis and Patent Owner Regeneron Regarding Discovery
1071	Transcript of Bench Trial (June 12, 2023) in Regeneron Pharms., Inc. v. Mylan Pharms. Inc., No. 22-cv-00061-TSK (N.D.W. Va. January 31, 2024) (ECF No. 558)
1072	Transcript of Bench Trial (June 20, 2023) in Regeneron Pharms., Inc. v. Mylan Pharms. Inc., No. 22-cv-00061-TSK (N.D.W. Va. January 31, 2024) (ECF No. 564)
1073	Transcript of Bench Trial (June 21, 2023) in Regeneron Pharms., Inc. v. Mylan Pharms. Inc., No. 22-cv-00061-TSK (N.D.W. Va. January 31, 2024) (ECF No. 566)
1074	Partial Transcript of Yancopoulos Deposition in Regeneron Pharms., Inc. v. Mylan Pharms. Inc., No. 22-cv-00061-TSK (N.D.W. Va. January 31, 2024) (ECF No. 624) (REDACTED)
1075	Transcript of Karen Chu Deposition in Regeneron Pharms., Inc. v. Mylan Pharms. Inc., No. 22-cv-00061-TSK (N.D.W. Va. January 31, 2024) (ECF No. 432-12)
1076	Deposition Transcript of Michael W. Stewart, M.D. (May 30, 2024) in IPR2023-00884

Exhibit	Description
1077	Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol. 2008 May;92(5):667-8.
1078	Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006 Oct 5;355(14):1432-44. (“ANCHOR Study”)
1079	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 (“MARINA Study”)
1087	Nguyen QD, Tatlipinar S, Shah SM, Haller JA, Quinlan E, Sung J, Zimmer-Galler I, Do DV, Campochiaro PA. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. Am J Ophthalmol. 2006 Dec;142(6):961-9.

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. In my prior declaration in this matter, I was asked to provide my opinions related to U.S. Patent No. 11,253,572 (“the ’572 patent”) (Ex. 1001) and the scientific and technical knowledge regarding the subject matter of the ’572 patent before January 2011.

3. I understand from counsel that Regeneron Pharmaceuticals, Inc. (“Patent Owner” or “Regeneron”) alleges that references with publication dates after mid-November should not be considered prior art. In particular, I understand that Regeneron alleges that the 2010 ARVO Abstract (Ex.1010), the December 2010 PR (Ex.1006), and the November 2010 PR (Ex.1007) are not prior art.

4. I understand Dr. Stewart provided a report assuming this is true, and I have also been asked to assume for the purposes of my report that this is true, and to

provide an updated summary of my opinions in response to his report.

5. I understand that if the 2010 ARVO and the December 2010 and November 2010 PRs are not prior art, they cannot properly be considered in the obviousness analysis or form the basis of an anticipation challenge. As set out further below, however, I confirm that my ultimate opinions regarding the obviousness of the claims of the '572 patent do not change even if references with publication dates after mid-November 2010 are not considered.

II. BACKGROUND AND QUALIFICATIONS

6. I set forth my background and qualifications in my prior declaration, which I incorporate into this section.

III. INFORMATION RELIED UPON

7. The opinions I provide in this proceeding are based on my general knowledge gained as a result of my education and experience as an ophthalmologist. In my prior declaration, I set forth the initial set of materials I considered in forming my opinions, which I incorporate into this section.

8. I have further reviewed and considered, among other things, additional records developed throughout this proceeding, including certain materials submitted by Patent Owner in support of its position and associated exhibits and declarations thereto.

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

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

IV. RESPONSE TO DR. STEWART & UPDATED SUMMARY OF OPINIONS

A. A POSA Would Have Considered It Obvious That Some Patients Would Achieve and Maintain to Week 52 the Recited Gains Based on Pre-November 2010 Art

11. I understand that Dr. Stewart does not contest that a prior art dosing regimen for treating AMD patients, consisting of three monthly loading doses of 2.0 mg aflibercept, followed by 8-week maintenance dosing was in the prior art well before 2010, as reflected in Dixon. I confirm that based on the pre-November 2010 art—specifically Dixon and the 2006 PR—a POSA would have reasonably concluded that some patients treated with that regimen would achieve and maintain the gains recited in the patent claims—i.e. 8-9 letter gains—including to week 52.

12. I understand that Dr. Stewart contends that the data available as of 2010 was not sufficient to predict the results of the VIEW clinical trials that used the relevant dosing regimen. Ex. 2065, ¶¶75-95. Whether the data could predict the result of a clinical trial, however, does not resolve for me the question of whether a

POSA would find it obvious that “a patient” (as recited in the ’572 patent claims) would achieve and maintain the relevant gains.

13. Contrary to Dr. Stewart’s opinion, given the volume and type of data regarding aflibercept available to a POSA as of 2010—as reflected in Dixon’s excellent summary and the 2006 PR—a POSA could make reasonable conclusions about whether some patients treated with the relevant VIEW dosing regimen would achieve and maintain the sorts of gains that had already become standard with anti-VEGF agents without a full clinical trial.

14. In particular, as of November 2010, aflibercept had been extensively studied. Regeneron had completed Phase I and II aflibercept trials, the details of which were summarized by Dixon and further reported in detail in the art at the time. Ex.1009; Ex.1027; Ex.2047.

15. First, as Dixon reports, Regeneron had completed by 2010 a Phase I AMD trial, the results of which were reported in the 2006 PR. In that trial, a single 2 mg or 4 mg dose in AMD patients produced a “mean improvement in BCVA [] 13.5 letters, with three of six patients gaining 15 or more letters” at six weeks. Ex.1027, 2; Ex.1009, 1575.

16. I understand that Dr. Stewart criticized this data for failing to separate out the results from the 2 mg and 4 mg groups. Ex.2065, ¶84. However, I understand that Regeneron itself reported the two dosing groups together, which would have

indicated to a POSA that there was not a significant difference in the gains between the groups. Ex.1027, 2; Ex.1028. In fact, consistent with this understanding, POSAs understood the CLEAR-IT-2 data discussed below to show a negligible difference in efficacy between the 2 mg and 4 mg groups.

17. Second, Dixon also describes the Phase II CLEAR-IT-2 results, which confirmed that the initial gains from 2 mg aflibercept could be sustained to at least 52 weeks in AMD patients with far less than monthly loading dosing.

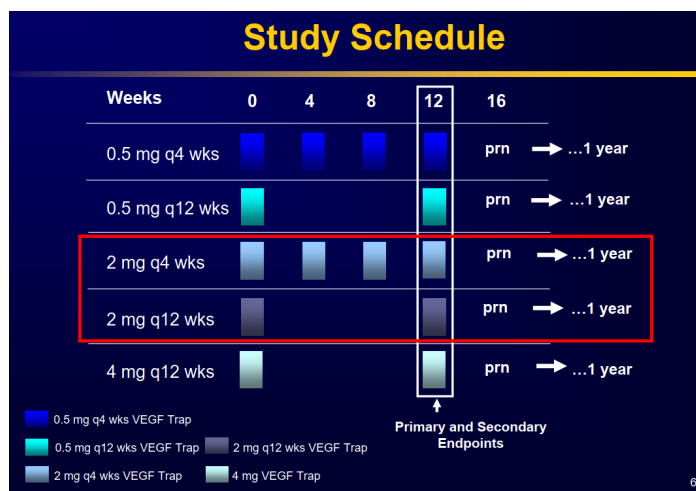
18. I understand that Dr. Stewart states that a POSA would not have expected that the extended dosing regimen would succeed based on Dixon because there was “limited information about the CLEAR-IT-2 Phase II clinical trial.” Ex.2065, ¶87. However, a POSA would have been aware, if they were curious about the strength of the numbers reported in Dixon, that more detail was available in the art. For instance, Dixon references a 2008 presentation given at Retina Society Annual Scientific Meeting in describing the CLEAR-IT 2 trial results. Ex.1009, 1576, 1579 (Reference 45). A POSA would have been aware of the details of the CLEAR-IT 2 trial results.

19. In fact, although it appears Dr. Stewart did not consider it, I understand Regeneron submitted that presentation as Ex. 2047 with its Patent Owner Preliminary Response, and described it as “VEGF Trap-Eye in Wet AMD - CLEAR-

IT 2: Summary of One-Year Key Results, Presented at 2008 Retina Society Meeting, Scottsdale, Arizona (Sep. 28, 2008).”

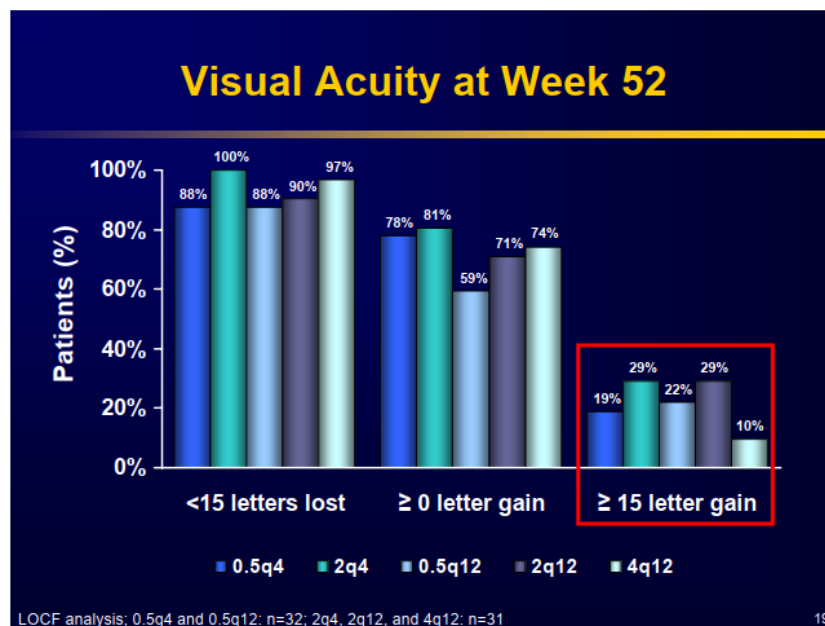
20. Ex. 2047 provides the data that Dr. Stewart calls out as missing, including results within 24 weeks, how many subjects were in the 2.0 mg dose group discussed in Dixon, and significant information regarding the timing of the doses given.

21. Specifically, as reported in Ex. 2047 and Dixon, the Phase II CLEAR-IT-2 investigated several aflibercept dosing regimens, with fixed loading doses (0.5, 2, or 4 mg) in the first 12 weeks on a quarterly or monthly regimen, followed by an assessment based PRN period until the 1-year mark. A summary of the investigated dosing arms is provided below:



Ex.2047, 6 (2q4 corresponds to a dosing arm with monthly loading doses through 12 weeks + PRN using 2 mg aflibercept; 2q12 corresponds a dosing arm with quarterly loading doses through 12 weeks + PRN using 2 mg aflibercept).

22. As reported, in the monthly loading dosing arm (2q4), the patients received four 2 mg monthly loading doses, but on average only ~5.6 doses over 52 weeks, with some patients requiring zero injections after the first four doses. Ex.1009, 1576; Ex.2047, 12-13. Further, the average time to first re-injection was over 85 days (approximately three months) for all cohorts. Ex.2047, 12-13. The data also shows that retinal thickness and visual acuity substantially improved with three monthly loading doses of 2 mg aflibercept. *See, id.*, 17-18. And in the quarterly loading dosing arm (2q12), patients received even fewer doses over 52 weeks (~4.5 doses), yet 29% of them still achieved gains of 15 or more letters, confirming the durability of aflibercept's efficacy over time. *Id.*, 19. A summary of the visual acuity results of the CLEAR-IT-2 trial at week 52 is provided below.



Regeneron Pharmaceuticals, Inc. Exhibit 2047 Page 19
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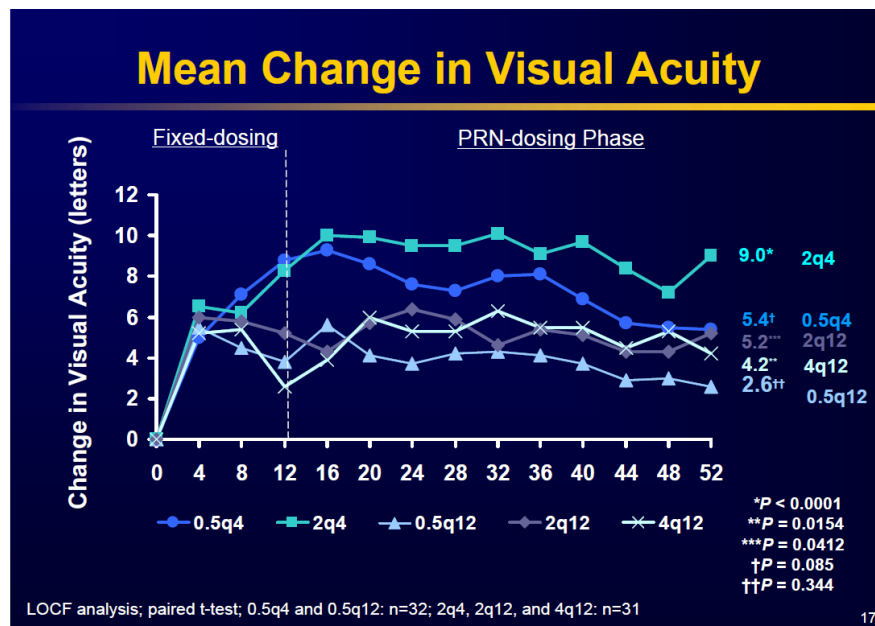
Ex.2047, 19.

23. Overall, based on these results, a POSA would have understood that a patient receiving three loading doses and five 8-week doses (8 in total) as recited would be more likely to sustain the gains because they would receive at least two more doses than in CLEAR-IT-2 whether measured as a mean or median. Ex.2047, 6, 12, 18-19. This is further reinforced by the fact that the CLEAR-IT-2 dosing arms achieved these results with fewer loading doses *and* fewer doses during the maintenance period than the recited dosing regimen. *Id.*

24. This is consistent with Dr. Stewart's acknowledgement that the CLEAR-IT-2 data demonstrated to POSAs that aflibercept maintained its effect for at least 8-week intervals, and confirmed the feasibility of an extended dosing for aflibercept. Ex.1076, 78:23-81:16. Specifically, the results reported that "[a]t 12 weeks VEGF Trap-Eye [aflibercept]...[m]aintained effect on visual acuity with a single dose to 8 weeks" equivalent to the clinical effect two monthly doses (at time zero and four weeks) produced at 8 weeks. *Id.*; Ex.2047, 17. Consistent with this understanding, Dr. Stewart published an article in 2008 suggesting that aflibercept would maintain biological efficacy for 10-12 weeks and would be capable of less frequent dosing. Ex.1077; Ex.1076, 58:1-63:4, 149:5-151:16.

25. Additionally, in my opinion, the CLEAR-IT 2 data further confirmed that there was no particular benefit to using 4 mg over 2 mg dose of aflibercept, at least for some patients. As shown above, the quarterly dosing arm with 4 mg of

aflibercept achieved the lowest percentage of patients with 15+ letter gains. Ex.2047, 19. In contrast, the 2 mg quarterly dosing arm and the monthly dosing arms had the highest percentage of patients achieving these gains. *Id.* In fact, as shown below, the 2 mg dosing arms generally had **higher** gains than the 4 mg dosing arm through 52 weeks.



Ex. 2047, 17.

26. Based on those results, a POSA would have found it obvious and expected that the 2 mg dose of aflibercept would have similar or better outcomes than the 4 mg dose at least for some patients.

27. The reported CLEAR-IT-2 data therefore reflects a POSA's understanding that it was obvious for some patients to achieve and maintain gains through 52 weeks on an extended dosing schedule as described in the prior art.

Although I do not think the details of the CLEAR-IT-2 data in Ex. 2047 would have been necessary to reach that conclusion, it was available to confirm the strength of the numbers reported in Dixon.

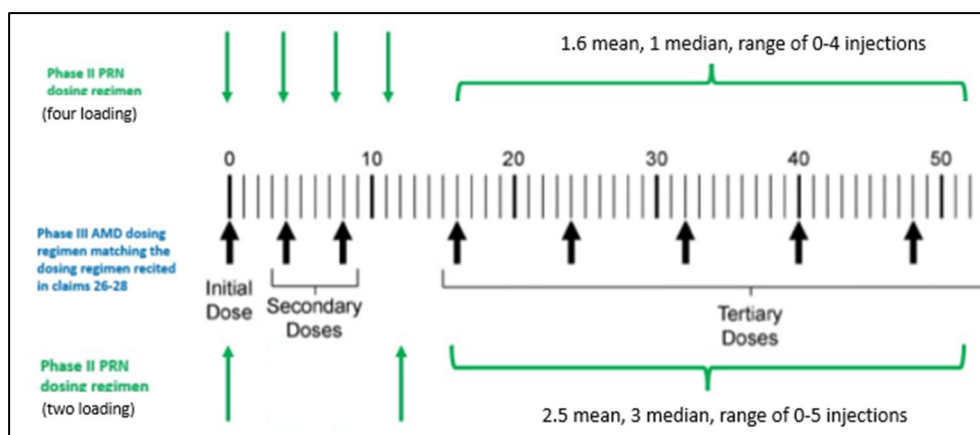
28. Based on the Phase I and Phase II trial data, POSAs also understood that Regeneron was moving forward with the VIEW 1 regimen in a Phase III trial with the secondary endpoint of the VIEW 1/2 study for AMD was the “proportion of patients who gained at least 15 letters of vision at week 52” as measured by ETDRS. Ex.1009, 1573, 1576-1578; Ex.1005, 1.

29. Though a POSA would not necessarily conclude the Phase III trial would hit this endpoint (though to my knowledge there was no significant information suggesting it would not), based on the clinical results discussed above, a POSA would have understood at least some patients would hit the endpoint.

30. I understand that Dr. Stewart focuses on the fact that POSAs would have been aware of other drugs that failed Phase III trials. Ex. 2065, ¶137. I agree this is true, but simply because a prior clinical trial failed to meet prespecified statistical endpoints for the treated cohort as a whole, that does not mean some patients did not receive a substantial benefit. The more salient fact informing my opinion, when asking whether some patients would get a gain, is that in all of the major ranibizumab trials (ANCHOR, MARINA, and PIER), at least 10% of patients sustained gains of 15+ letters (the secondary endpoint). Ex.1078, 1432, 1437 (Fig.

1.B); Ex.1079, 1425 (Fig. 1.D) ; Ex.1021, 243 (Fig. 2). In the PIER study involving three loading doses followed by every 12-week dosing, for instance, which Dr. Stewart characterizes as a “failed” study, 13% of patients achieved and sustained 15+ letter gains through week 52. Ex.1021, 243 (Fig. 2). In view of a POSA’s understanding that aflibercept was “the most promising anti-VEGF investigational drug” that “may have longer duration of effect in the eye” than other anti-VEGF drugs at the time, a POSA would have expected that aflibercept would produce a comparable or better outcomes than those shown in these prior clinical trials, at least for some patients.

31. I understand that Dr. Stewart also suggests that a POSA would not have believed that results from a protocol of four loading doses or two loading doses would have predicted anything about the results of a protocol with three loading doses. In my opinion, this ignores that the loading doses in CLEAR-IT-2 bracketed the number of Dixon’s loading doses, as shown below:



32. Specifically, the 2q4 dosing arm in the CLEAR-IT-2 trial required four loading doses whereas 2q12 required two loading doses by the 12 week mark. Both of these dosing arms achieved 15+ letter gains in 29% of patients by 52 weeks. Ex. 2047, 19. Therefore, it would have been obvious to a POSA that the differences in the loading doses (three versus two or four) would not prevent at least some patients from achieving 15+ letter gains by week 52, given the results reported for the two groups bracketing the 3 loading doses achieved substantial visual acuity gains over 15 letters.

33. In my opinion, this expectation was further confirmed by Regeneron's decision to move forward in the Phase III AMD trial with three loading doses, rather than four or two, which was disclosed in Dixon. Ex. 1009, 1573, 1576-1578; Ex. 1005, 1. A POSA would have understood, as Regeneron did, there was a sound scientific basis for expecting that at least some patients would succeed in achieving the recited efficacy with an extended dosing regimen comprising three loading doses.

B. A POSA Would Have Considered It Obvious That Some DME Patients Would Achieve The Recited Gains Within 24 Weeks Based On Pre-November 2010 Art

34. I understand that Dr. Stewart does not contest that a prior art dosing regimen for treating DME patients, consisting of three monthly loading doses of 2.0 mg aflibercept, followed by 8-week maintenance dosing was in the prior art well before 2010, as reflected in the 2009 PR. I confirm that based on the pre-November

2010 art—specifically the 2009 PR (Ex. 1005), Dixon (Ex. 1009), and the 2007 ARVO Abstract (Ex. 1030)—a POSA would have reasonably concluded that some patients treated with the prior art regimen would achieve and maintain the gains recited in the patent claims within 24 weeks—i.e. 8-9 letter gains.

35. As with the prior section, I understand that Dr. Stewart contends that the data available as of 2010 was not sufficient to predict the results of the DA VINCI clinical trial that used the relevant dosing regimen. Ex.2065, ¶¶98-102. As before, whether the data could predict the result of a clinical trial, however, does not resolve the question of whether a POSA would find it obvious that “a patient” (as recited in the ’572 claims) would achieve the relevant gains. Contrary to Dr. Stewart’s opinion, given the volume and type of data regarding aflibercept available to a POSA as of 2010—as reflected in the 2009 PR, Dixon, and the 2007 ARVO Abstract—a POSA could make reasonable conclusions without a full clinical trial about whether some patients treated with the relevant DA VINCI dosing regimen would achieve and maintain the sorts of gains that had become standard with anti-VEGF agents.

36. First, specifically, it was known from the Phase I DME trial of aflibercept that a single 4 mg dose in DME patients produced a “9 letters [gain in EDTRS] at four weeks....” Ex.1009, 1575; Ex.1030 (“Four patients had improvements in BCVA, ranging from 6 to 10 letters at 4 weeks post-injection.”);

Ex.1002, ¶189. I understand that Dr. Stewart contends that “[n]o POSA would have drawn conclusions about the efficacy of a 2 mg dose from the result of a trial involving a 4 mg dose.” I disagree.

37. Dr. Stewart disregards important context. In my opinion, a POSA would have reasonably expected a similar gain would be produced by an initial set of three 2 mg loading doses in DME than AMD patients. As I previously explained, POSAs understood that AMD and DME had a similar mechanism of action, and would expect similar gains, as had already been shown in the various clinical trials. *See* Ex.1002, ¶¶43-49, 188. As with AMD, it was well known that “VEGF...plays a major role in DME,” thus a POSA would have reasonably expected that blocking the VEGF signal would produce clinical benefit in the treatment of DME as it did AMD. Ex. 1087, 968.

38. Indeed, a single dose of 4 mg aflibercept maintained 9 letter gains for DME patients through week 4 (Ex.1009, 1575), which was better than 5 letter gains achieved with a single dose of 4 mg aflibercept in AMD patients during the same time frame. Ex.2047, 17 (*see* ¶25 above). This direct comparison of a single 4 mg dose of aflibercept in AMD versus DME would have suggested to a POSA that aflibercept would achieve similar clinical benefits in DME as in AMD for some patients. Therefore, a POSA applying an initial set of three 2 mg monthly loading doses to some DME patients according to the DA VINCI dosing regimen would

have expected similar clinical benefits to what was shown through the three loading doses in the CLEAR-IT-2 trial in AMD patients (i.e., greater than 9 letter gains). *See* Ex.2047, 17.¹

39. Moreover, a POSA would have also recognized that there was not a discernible difference in efficacy between 2 mg and 4 mg doses of aflibercept in the CLEAR-IT-2 trial such that a POSA expected a single dose of 2 mg aflibercept to achieve a clinical benefit as a single 4 mg dose in some DME patients. Ex.2047, 17.

40. First, the 2009 PR taught that in the Phase II DME study, Regeneron was proceeding with a 2 mg and a 0.5 mg dose, not a 4 mg dose. Ex. 1005. Based on this disclosure, a POSA would have understood that there was not an expected difference in the likely efficacy of the 2 mg and 4 mg doses, at least for some patients, as it would not make logical sense for Regeneron to proceed to a Phase II DME study with only the 2 mg dose unless it expected gains at least as good as what it obtained in the CLEAR-IT-2 trial and had been established with ranibizumab (i.e. at least 8-9 letters).

¹ Although the results show a mean gain slightly over 8 letters, since visual acuity gains are measured in whole numbers, a POSA would interpret the data as indicating that at least some AMD patients achieved gains of over 9 letters by week 12. Ex.2047, 17.

41. The known pharmacokinetics of aflibercept also support the conclusion that 2 mg dose would work as well as the 4 mg dose did in the context of the proposed DA VINCI dosing regimen. Before 2010, Dr. Stewart himself calculated that the half-life of aflibercept was roughly 4-5 days. Ex.1077. This means that after roughly 4-5 days, a 4 mg injection would become a 2 mg injection in the eye—in other words, the effective period of a 4 mg injection would be shortened by roughly 4-5 days if changed to a 2 mg injection. *Id.* As he explained it, this meant that “[a]fter injection of 0.5, 2 and 4 mg VEGF Trap, the intravitreal VEGF-binding activities (comparable to ranibizumab at 30 days) would occur at 73, 83 and 87 days, respectively.” *Id.*, 667. Given POSAs had concluded that aflibercept had effectiveness to at least 8 weeks, and further that in the relevant dosing regimen, they would receive the initial doses only 4 weeks (28 days) apart for the first three doses (and 8 weeks apart for the remainder (56 days)), a POSA would not conclude that the loss of 4-5 days from the effective period would meaningfully impact the efficacy. This conclusion would have further been confirmed by the CLEAR-IT-2 data, which showed that the 4 mg dose did not increase efficacy as discussed above.

42. Finally, I note that POSAs would have been aware that DME patients had already achieved 9-letter gains within 24 weeks in multiple trials involving the inferior ranibizumab molecule. *See, e.g.*, Ex.1087, 966 (Phase I trial of ranibizumab achieving a mean letter gain well over 9 letters through month 6); Ex.1018, 1069.

The gains in question, in other words, were not unknown, and as discussed above, a POSA would have reasonably concluded that the superior aflibercept molecule would match and exceed those gains, at least in some patients. Ex.1009, 1577.



June 10, 2024

Date

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