

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD., CELLTRION, INC.,
and BIOCON BIOLOGICS INC.,
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00884¹

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

**PETITIONER'S REPLY TO
PATENT OWNER'S RESPONSE**

¹ IPR2024-00260 and IPR2024-00298 are joined with IPR2023-00884.

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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”)
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”)

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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. Drugs R D. 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. Ophthalmology. 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. 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”)
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.e

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	du/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-online.com/displayfilinginfo.aspx?FilingID=4380124-5423-15279&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6 (“May 2006 Press Release”)

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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”)
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1035	Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A. 2002;99(17):11393-11398 (“Holash”)
1036	Rudge JS, Thurston G, Davis S, et al. VEGF trap as a novel antiangiogenic treatment currently in clinical trials for cancer and eye diseases, and VelociGene- based discovery of the next generation of angiogenesis targets. Cold Spring Harb Symp Quant Biol. 2005;70:411-418 (“Rudge 2005”)

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

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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”)
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1052	Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006; 355(14):1419-31 (“Rosenfeld 2006”)
1053	Heimann, H. (2007). Chapter 5 Intravitreal Injections: Techniques and Sequelae. In: Holz, F.G., Spaide, R.F. (eds) Medical Retina. Essentials in Ophthalmology. Springer, Berlin, Heidelberg (“Heimann 2007”)
1054	Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreal injection: a comprehensive review. Retina. 2004;24(5):676-698 (“Jager 2004”)
1055	Certified Prosecution History of U.S. Patent No. 10,130,681 B2 (“‘681 patent PH”)
1056	Pilot Study of Intravitreal Injection of Ranibizumab for Macular Telangiectasia With Neovascularization (NCT00685854) (May 24, 2008), available at:

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

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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
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”)

Exhibit	Description
1080	Deposition Transcript of George D. Yancopoulos, M.D., Ph.D. (April 12, 2024) in IPR2023-00884
1081	Samsung Bioepis Petition for IPR filed in <i>Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.</i> , PTAB-IPR2023-00739 (Paper 1) (“Samsung 601 Petition”)
1082	Deposition Transcript of Karen Chu (April 11, 2024)
1083	RGN-EYLEA-MYLAN-00526220 - RGN-EYLEA-MYLAN-00526223
1084	Deposition Transcript of Richard Manning, Ph.D. (March 27, 2024) in <i>Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.</i> , PTAB-IPR2023-00739 and -00884
1085	Deposition Transcript of Michael W. Stewart, M.D. (March 29, 2024) in <i>Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.</i> , PTAB-IPR2023-00739
1086	Memorandum Opinion and Order Following Bench Trial, <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 22-cv-00061-TSK (N.D.W. Va. January 31, 2024) (ECF No. 692) (REDACTED)
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. <i>Am J Ophthalmol.</i> 2006 Dec;142(6):961-9
1088	Institution Decision issued in <i>Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.</i> , PTAB-IPR2023-00739 (Paper 9) (“601 IPR ID”)
1089	Declaration of Michael W. Stewart, M.D. submitted as Exhibit 2027 in <i>Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.</i> , PTAB-IPR2023-00739 (“Stewart ’601 IPR Decl.”)
1090	Patent Owner Response submitted as Exhibit 2027 in <i>Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.</i> , PTAB-IPR2023-00739 (“601 IPR POR”)
1091	RGN-EYLEA-MYLAN-00631182
1092	Responsive Expert Declaration of Dr. Edward Chaum, dated June 10, 2024 (“Chaum Resp. Decl.”)

I. INTRODUCTION

Samsung Bioepis Co., Ltd. (“Petitioner”) seeks cancellation of claims 1-30 (the “Challenged Claims”) of U.S. Patent No. 11,253,572 (“’572 patent”) (Ex.1001), assigned to Patent Owner (“PO”).

One subset of the Challenged Claims—claims 1-14 and 26-30—recite a dosing regimen for angiogenic eye disorders, along with general or specific visual acuity gains. Grounds IV, VI, VIII are based on Dixon as a primary reference and are directed to those claims. They are addressed in Section II.A below.

A second subset of the Challenged Claims—claims 15-25—are directed to a dosing regimen for DME specifically. Some of these claims recite visual acuity results or a specified number of doses. Grounds I, V, VII, and IX are all based on the 2009 Press Release (“PR”) as a primary reference, and address claims 15-25. They are addressed in Section II.B below.²

² Consistent with the Board’s instruction to simplify its presentation, Petitioner notes the Board need not consider the references that PO contends are not prior art (*i.e.*, ARVO 2010 and the November/December 2010 PRs) in order to find all Challenged Claims obvious, as set out in connection with Grounds I and IV-IX below. Thus Petitioner has omitted discussion of them from those Grounds. Should

With the exception of a single claim (claim 25, directed to five loading doses), there is no dispute that the prior art discloses the dosing regimens recited in both claim subsets—the core of the alleged inventions—or that there was motivation to adopt them to treat AMD and DME.³ Furthermore, as the prior art shows, anti-VEGF agents, and aflibercept in particular, had already produced visual acuity gains in patients far superior to the modest gains recited in the claims. Indeed, while the Challenged Claims recite a maximum gain of 9 letters for a patient at 52 weeks, aflibercept had already been shown to produce gains of 15+ letters through 52 weeks. These 15+ letter gains were achieved with treatment that included substantially fewer doses through 52 weeks—both loading and maintenance—than a patient would receive in the prior art regimens on which Petitioner relies.

The premise of PO’s response is that, allegedly, “none of those references reliably indicate the outcome of the planned Phase III trials.” POR, 39. But that is not the relevant question. “What matters is the objective reach of the claim.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). Here, the objective reach of the claims do not require an entire patient population to achieve the recited gain on

the Board reject PO’s attempt to antedate, those references could be considered as further confirming the Challenged Claims’ obviousness.

³ PO does not contest Ground I (claims 15 and 24). POR, fn. 5.

average. They are directed to methods for treating “a patient.” “Nothing in the claims requires that the regimen be used for—let alone be ideal for—the patient population generally or a certain percentage of the patient population.” *Janssen Pharmaceuticals, Inc. v. Teva Pharmaceuticals, USA, Inc.*, 97 F.4th 915, 926 (Fed. Cir. 2024). Thus, “[g]iven the scope of the claims here, it [is] important... to recognize the distinction and focus... on single patient administration.” *Id.*

Given the low hurdle set by the recited gains and the extraordinary and sustained effect on angiogenic diseases that anti-VEGF agents, including aflibercept, were already having on individual patients, a POSA would have reasonably concluded that at least some patients would achieve the recited gains. That is sufficient to resolve Grounds I and IV-IX, covering all Challenged Claims.

Because the Board should find the claims invalid as obvious, it need not reach the remaining anticipation grounds (Grounds II-III), set out in Section II.C. These grounds turn solely on Petitioner’s attempt to antedate. But should the Board reach them, it should find PO failed to make the fundamental showing necessary to antedate the art—that Dr. Yancopoulos was the first person to conceive of the dosing regimen used in these trials. Nor did PO show that the work done by Bayer and PO and reported in the prior art was on Dr. Yancopoulos’s “behalf,” as PO alleges. Accordingly, the claims are invalid on these additional grounds as well.

Finally, as set out in Section II.D, Petitioner requests that the Board reconsider its decision to give patentable weight to the claimed efficacy limitations, and thus find unpatentability under Grounds X and XI.

II. THE CHALLENGED CLAIMS ARE OBVIOUS

In response to the Petition, rather than taking on the disclosures of the prior art, PO sets out a strawman test—whether individual data points in the references, taken alone, were predictive of the ultimate Phase III trial results. PO’s response thus runs “afoul of KSR’s basic mandate in a number of ways” by “failing to consider the interrelated teachings of multiple references, the background knowledge possessed by a person having ordinary skill in the art, or the inferences and creative steps that a person of ordinary skill in the art would employ.” *Janssen*, 97 F.4th at 931 (cleaned up). But as the Board already correctly found, a POSA would “have looked across the breadth of clinical trials” in the prior art to “identify the results of administering 2 mg of aflibercept in the manner claimed in the ’572 patent.” ID, 55-56. That analysis shows the claims are obvious, as set out below.

A. Grounds IV, VI, VIII: Dixon/2006 PR and Generic/AMD Results Claims⁴

Claims 1-5, 8-11, and 26-30 are directed to methods of treating a patient with an angiogenic disorder or AMD using monthly loading doses/8-week maintenance doses, with additional limitations directed to particular visual acuity gains within or at certain timepoints. PO does not dispute that Dixon discloses a dosing regimen that meets the requirements of the claims challenged in these Grounds. The parties’ only significant dispute is whether Dixon in view of the 2006 PR renders the “results limitations” of claims 1-5, 8-11, and 26-30 obvious. It does. Ex.1092, ¶¶11-33.

1. Ground IV

(a) Claims 1-5 and 8-11

Claims 1-5, 8-11, and 26-30 are rendered obvious by Dixon in view of the 2006 PR. The narrowest of claims 1-5 and 8-11 require that “the patient gains at least 9 letters” *within* 24 weeks or 52 weeks. Ex.1001, 23:15-27, 32-44.

A 9-letter gain within 24 or 52 weeks was obvious. Dixon describes (1) the Phase I trial, the results of which showed that a single 2mg or 4mg dose in AMD

⁴ The only issue of claim construction raised by PO (at 3-4) is that the Challenged Claims allegedly recite a “fixed” or “predetermined” regimen. The Board should reject this argument for the reasons stated in the ’601 Institution Decision. *See, e.g.*, Ex.1088, 39-42.

patients produced a mean gain of 13.5 letters; and (2) the CLEAR-IT-2 trial, which showed AMD patients maintained a ***mean gain of 9 letters by 52 weeks, with 29% gaining 15+ letters***. Ex.1009, 1576; *see also* Ex.1002, ¶173. As PO’s expert testified, POSAs understood that the majority of patients achieve their gains in the first 24 weeks (Ex.1089, 71:16-72:5), and the underlying CLEAR-IT-2 data shows these gains were in fact made within the first 24 weeks (Ex.2047, 16-17), consistent with that testimony.

PO challenges this conclusion not by taking on the disclosures of the prior art as a whole, but by picking at individual data points in the reported clinical trial results to suggest that, in its words (at 39), “none of those references reliably indicate the outcome of the planned Phase III trials.” But that is not the test, and PO’s arguments ignore the context of the art and a POSA’s knowledge.

For instance, PO argues (at 39-40) that a POSA would ignore the Phase I data because it reports combined results for the 2mg and 4mg groups. But PO itself reported the results together, indicating there was not a significant difference in the gains between the groups such that reporting needed to be separate. Ex.1027, 2; Ex.1092, ¶¶11-16.

Similarly, PO (at 42) complains that Dixon’s CLEAR-IT-2 data is incomplete as to details like granular sample size, and thus cannot be used to predict the Phase III trial results. But PO itself submitted a presentation it acknowledges was presented

in 2008 and contained the complete CLEAR-IT-2 data (*see* Ex.2047; POPR, vii) — clearly material that would have been part of “the background knowledge possessed by a person having ordinary skill in the art.” *Janssen*, 97 F.4th at 931; *KSR*, 550 U.S. at 418; Ex.2047; Ex.1092, ¶¶17-19. Regardless, a POSA would not need such detail to conclude the claims were obvious, because what is required is not a definitive prediction that the Phase III trials would succeed across a particular patient population—just that the regimen would produce the modest recited gains in at least some patients. Ex.1092, ¶¶11-33.

PO further argues (43) that a POSA would not have drawn conclusions based on the Phase II trial data because “the POSA would have known that Phase III trials regularly fail.” This is a strawman. A POSA would understand that even though Phase III trials might fail to hit their endpoints, individual patients within those trials would still receive substantial benefits consistent with the endpoint. Ex.1092, ¶30.

Finally, PO’s attempt to reframe Petitioner’s ground as “a disguised inherency argument” is baseless. PO argues (47-50) that the Board misapplied *Mustek* and *Unwired Planet* in the ID because Petitioner does not “point[] to any actual disclosure of the claimed result in the prior art.” That is false. Petitioner points to existing results in the art and explains why a POSA would reasonably conclude that they would be produced by the prior art dosing regimens. The Board properly recognized this distinction. ID, 56-57.

(b) **Claims 26-30**

Claims 26-30 are rendered obvious by Dixon in view of the 2006 PR. Claims 26-30 recite the claimed method is “as effective in [achieving a gain in or maintaining visual acuity]” as monthly administration of 0.5 mg ranibizumab “at 52 weeks.” Ex.1001, 24:26-25:5. PO’s expert acknowledged that a 8-9 letter gain sustained to 52 weeks is sufficient to meet these limitations. Ex.1076, 14:13-16:12.

A POSA would have reasonably concluded that a three-loading dose/8-week maintenance regimen would sustain such a gain to 52 weeks for at least some patients. This is not a case where the recited gains were unknown. Indeed, Dixon reports that CLEAR-IT-2 “study data... demonstrated stabilization of [patient’s] vision that *was similar to previous studies of ranibizumab at 1 year*,” including the ANCHOR and MARINA trials that studied monthly administration of 0.5 mg ranibizumab. Ex.1009, 1576-77. In fact, the CLEAR-IT-2 data showed that substantially *higher* gains of 15+ letters could be produced with fewer loading and maintenance doses, and further confirmed that 8-week interval dosing would be successful at maintaining gains. Ex.1092, ¶¶20-24.

Specifically, as reported in Dixon, nearly 30% of patients achieved gains of 15+ letters at 52 weeks, including for the arms that that received only two loading doses (2q12) and those who received four (2q4). Ex.1009, 1576; Ex.1002, ¶¶180-181; Ex.2047, 19. Moreover, this CLEAR-IT-2 result was achieved in patients who

received both fewer loading doses **and** fewer doses during the maintenance period than patients on a three-loading dose/8-week maintenance regimen. Ex.1092, ¶¶20-24.

In addition, PO’s expert further acknowledged that POSAs understood that the CLEAR-IT-2 trial discussed in Dixon demonstrated that aflibercept maintained its effect for at least 8-week intervals (Ex.1076, 78:23-81:16)—the longest intervals between doses in the relevant 3-loading dose/8-week maintenance regimen—further confirming that the CLEAR-IT-2 gains could be maintained to 52 weeks. Ex.1092, ¶¶24; Ex.2047, 9, 17. In fact, though not necessary to the conclusion, PO published a paper shortly after CLEAR-IT-2 admitting that the CLEAR-IT-2 data provided the “rationale for the 2mg q8wk dose” by showing that “the improvement in BCVA after a single 2-mg dose was similar to that obtained with 2 mg dosed monthly to 8 weeks....” Ex.1039, 7.⁵

In other words, the data in CLEAR-IT-2 showed that (as PO’s expert testified) patients made their gains in the first months of treatment, and that the 8-week interval

⁵ As PO’s expert further agreed, this extended efficacy aligned with prior art calculations showing aflibercept would maintain biological efficacy for 10-12 weeks—calculations that PO’s expert published, noting they supported less frequent aflibercept dosing. Ex.1077; Ex.1076, 58:1-63:4.

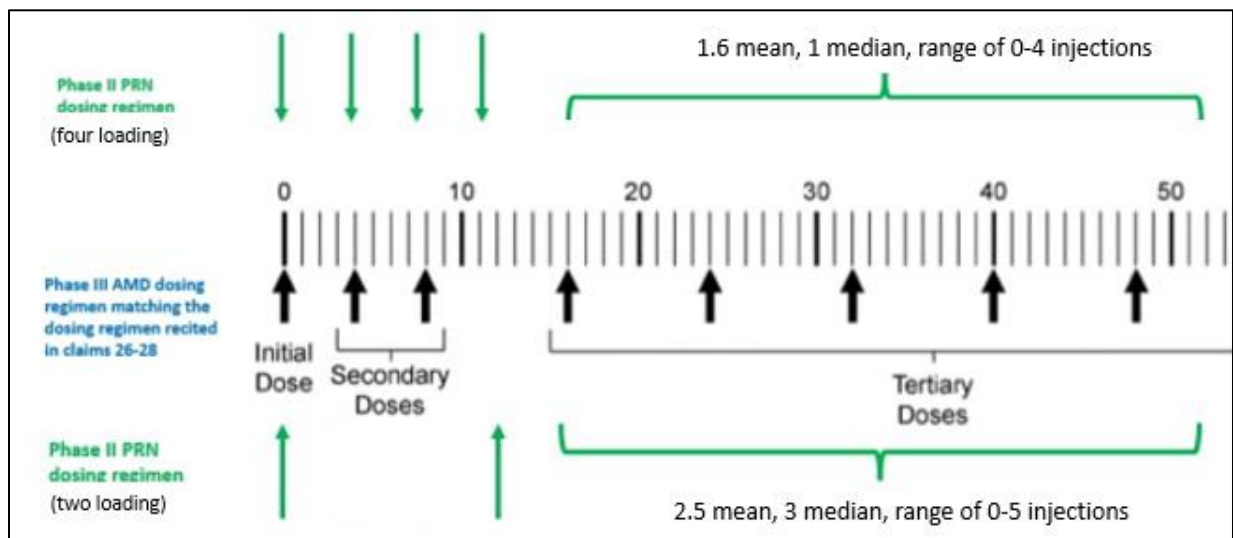
would maintain the effect—particularly given patients would receive more doses during the maintenance period than the CLEAR-IT-2 patients who maintained 15+ letter gains at week 52.

More broadly speaking, a POSA would have seen from Dixon that Regeneron had decided to move forward, based on the CLEAR-IT-2 results, with a 3 loading dose/8-week maintenance regimen in Phase III with a secondary endpoint of a 15+ letter gain at 52 weeks. Whether or not a POSA would conclude that the regimen was likely to meet the secondary endpoint across the entire population of patients, it would have been obvious that *some* patients would meet the endpoint based on Dixon and a POSA’s knowledge of the art. Ex.1092, ¶¶28-30. Indeed, *every major trial of an anti-VEGF* that extended to 52 weeks had shown that *at least 13% of patients sustained gains of 15+ letters to 52 weeks*, and generally substantially more, including the allegedly failed PIER trial’s quarterly dosing arm. Ex.1092, ¶30.

In fact, PO’s expert admitted that because of the natural course of disease progression, it is routine for sham treated patients to achieve 15+ letter gains by 52 weeks. Based on these gains, PO’s expert acknowledged that a POSA would have considered it more probable than not that a patient on a three-loading dose/8-week maintenance regimen would achieve 15 letter gains. Ex.1076, Ex.1076, 140:5-143:22, 117:22-119:20, 162:17-168:5 ; see Ex.1021.

PO suggests that the differences in the number of loading doses between the various regimens would have prevented a POSA from making any reasonable conclusions based on the Phase II results.

But a POSA would have understood that Regeneron’s decision to move forward in the Phase III AMD trial with three loading doses and a secondary endpoint of 15+ letters indicated that the differences in the loading doses (three versus two or four) would not prevent at least some patients from achieving the same 15+ letter gains achieved in CLEAR-IT-2, whether or not the endpoint was met for the trial. Ex.1009, 1573, 1576-1578; Ex.1092, ¶¶31-33. Indeed, the loading doses in CLEAR-IT-2 bracketed a three-loading-dose regimen, as shown below, demonstrating that regimens with both fewer and more loading doses were successful:



Id. Moreover, as shown above, a POSA would have understood that a patient receiving three loading doses and five 8-week doses 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.1092, ¶¶23-24; Ex.1009, 1576; Ex.2047. Indeed, the CLEAR-IT-2 data showed no patient in the relevant groups received more injections than would have been received by a 3-loading dose/8-week patient over 52 weeks. *Id.*

Taken together, in view of the knowledge of the art, a POSA would have viewed the data reflected Dixon as more than sufficient to reasonably conclude that some patients would achieve far more than a 9 letter gain by 52 weeks.

Additionally, as to claims 26 and 29-30 which do not require a specific number of loading doses, a POSA would have found it obvious to modify the Dixon dosing regimen to include additional initial doses, for the same reasons addressed in relation to claim 25—i.e. because such routine optimization was obvious. *See, e.g.*, Ex.1017, 23-24. It would have been obvious to a POSA that these regimens would succeed. PO’s expert admitted that, for instance, a POSA would expect success for some patients—meaning gains on par with ranibizumab or 15+ letter gains—using four or five monthly doses. Ex.1061, 142:20-143:1; Ex.1076, 183:16-185:4. In fact, PO’s expert acknowledged that an initial dose followed by 11 loading doses is within the scope of these claims. Ex.1076, 30:11-32:15. Modifying the dosing regimen to

provide additional initial loading doses (even monthly doses) would increase a POSA’s reasonable expectation of producing a gain as effective as monthly ranibizumab. *Id.*

2. Ground VI

Claims 6-7 and 12-13 additionally recite formulating aflibercept as an isotonic solution or with a nonionic surfactant. Dixon in view of the 2006 PR and Hecht render claims 6-7 and 12-13 obvious.

PO’s primary argument (at 59-60) is that the prior art suggested ophthalmic formulations *could be* non-isotonic and *may* include an ionic surfactant, and that this teaches away. But the art confirmed that “isotonicity always [was] desirable” for ophthalmic formulations and non-ionic surfactants were known to be the “least toxic to ophthalmic tissues” among other known benefits. Ex.1016, 1571; *see also*, Ex.1032, 159. There was no teaching away.

Additionally, PO contends (at 59) that Dr. Chaum’s testimony should be ignored because he “has no experience formulating drugs.” But Dr. Chaum testified that he understands the impact of tonicity and surfactants based on his training as an ophthalmologist. Ex.2090, 336:11-361:10. And the alleged inventor Dr. Yancopoulos is also not a drug formulator. Ex.1080, 44:17-47:2.

3. Ground VIII

PO does not contest the two exclusion criteria recited in claim 14 should not be given patentable weight. POR, 64. Accordingly, all elements of claim 14 are rendered obvious in view of Dixon.

B. Grounds V, VII, and IX: 2009 PR/DME Claims

1. Ground V

Claims 16-17, and 20-21 are rendered obvious by the 2009 PR in view of Dixon and the 2007 ARVO Abstract. Ex.1092, ¶¶34-42.

There is no dispute that the 2009 PR discloses a dosing regimen (3-loading/8-week maintenance) for DME that meets the dosing regimen limitations of the DME Results Claims. The narrowest of the claims require a DME patient to achieve a gain of 9 letters *within* 24 weeks during the recited dosing regimen.

A POSA would find it obvious that 2009 PR regimen would produce a 9 letter gain within 24 weeks in at least some patients. *See* Pet. 46-49; Ex.1002, ¶¶184. Specifically, it was known from the Phase I DME trial of aflibercept that a single 4mg dose in DME patients produced a “9 letters [gain in EDTRS] at four weeks....,” well before 24 weeks. Ex.1009, 1575; Ex.1030; Ex.1002, ¶189. Such gains were common from treatment of DME with an anti-VEGF. Indeed, +9 letter gains within 24 weeks for DME patients had been achieved with the inferior ranibizumab molecule in multiple clinical trials. Ex.1092, ¶42; Ex.1087, 966; Ex.1018, 1069. A POSA would have reasonably concluded the same gain would be produced by an

initial set of three 2mg loading doses, given the successful use of initial loading doses in the context of AMD trials. See Ex.1002, ¶¶43-49, 188 (explaining similar mechanism of action and results for AMD, DME); Ex.1092, ¶¶36-42.

PO (at 55) takes the position that “[n]o POSA would have drawn conclusions about the efficacy of a 2mg dose of aflibercept in DME patients” from these disclosures because the trial was a small Phase 1 trial. But inventor Dr. Yancopoulos himself published a paper stating the initial trials were evidence that “VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity....” Ex.1036, 414-15.

PO (at 55) also argues that no conclusions can be drawn from the 4mg results because they used “double the claimed 2mg dose.” In this regard, PO ignores the full context of the art, including substantial information indicating the 2mg dose would be at least as effective as the 4mg dose. Ex.1092, ¶¶36-42.

First, the 2009 PR teaches that in the Phase II study, PO was proceeding with a 2mg and a 0.5mg dose, **not** a 4mg dose. Ex.1005, 1. A POSA would have understood the decision to proceed only with a 2mg dose, and not a 4mg dose, to signal that the reduction in dose size would not reduce the established gains below those already produced with the 4mg dose. The CLEAR-IT-2 data supported this conclusion, showing no benefit from the 4mg dose over the 2mg dose in the context

of AMD, which shares a similar mechanism with DME. Ex.1092, ¶¶25-26; Ex.2063, ¶24 (Yancopoulos admitting “no clear benefit.”).

As PO contended throughout the ’601 patent IPR, POSAs would not accept efficacy lower than shown for monthly ranibizumab in treating DME, which it contended was 8-9 letters. Ex.1089, ¶¶73-77; Ex.1090, 36-37. The established gains from a single 4mg dose were consistent with those gains—i.e. at least 8-9 letters. Ex.1092, ¶40. It would make no sense to reduce the dose size from 4mg to 2mg when proceeding to an expensive Phase II trial if the change was expected to reduce efficacy such that it would produce worse results than ranibizumab.

Second, a POSA would have expected at least equivalence between multiple administrations of a 2mg dose and a single 4mg dose (for either AMD or DME) in view of the known pharmacokinetics of aflibercept. Ex.1092, ¶41. As Dixon and PO’s expert’s own work showed, the half-life of aflibercept in the eye was expected to be 3-5 days. Ex.1077. As Dr. Chaum explains, based on this, a POSA would have understood that a 4mg dose of aflibercept turned into 2mg within 3-5 days, and that because of this, a POSA would not “think that there would be a different response to a... 4 milligram injection versus a 2-milligram injection over the period of a month.... Because three days later its 2 milligrams in the eye.” Ex.2090, 392:1-5; Ex.1092, ¶41. Indeed, PO’s expert Dr. Stewart likewise concluded that the duration of binding activities between the 2mg and 4mg doses of aflibercept would be highly

similar, extending to 83 and 87 days, respectively—far longer than the monthly or 8-week intervals between doses in the relevant regimen. Ex.1077, 667.

Third, Dr. Chaum further explains that because DME and AMD share a similar mechanism of action, POSAs “recognized and expected that a treatment method that works for AMD would likely work for DME” and produce a similar outcome. Ex.1002, ¶188. As set out above, it was well established prior to 2010 that some AMD patients achieved gains far greater than 9 letters with a 2mg dose.

The Board should cancel the DME Results Claims.

2. Ground VII

Claims 18-19 and 22-23 are rendered obvious by the 2009 PR in view of the 2007 ARVO Abstract, Dixon, and Hecht. PO’s arguments regarding Hecht are the same as to these claims, and fail for the reasons addressed in Section II.A above.

3. Ground IX

Claim 25 is rendered obvious by the 2009 PR in view of Shams or Elman.

Claim 25 recites the same dosing regimen of the DME claims challenged in Petitioner’s ’601 IPR (IPR2023-00739). See Ex.1081. Petitioner presents the same Grounds here, and claim 25 is invalid for the same reasons.

As to Shams, PO (at 66-67) contends that a POSA would have ignored Shams because the PIER regimen “had been shown not to work.” But Shams is not limited to PIER and, regardless, PIER produced gains of 15+ letters in some patients.

Ex.1004, 247; Ex.1071, 78:24-85:5. PO’s position ignores the real import of Shams: POSAs understood that they could optimize the initial monthly doses. Ex.1002, 204-216.

As to Elman, PO contends (at 67) that Elman taught the use of six doses, not five. But even if Elman taught toward the use of six doses (it does not), the fact that Elman describes success in treating DME patients with such a narrow range of doses suggests the use of five initial loading doses. Ex.1002, ¶¶217-236.

As to both references, PO (at 68) contends that a POSA would not consider ranibizumab regimens. But a POSA reviewing the 2009 PR in view of Shams or Elman would have found it natural to adopt, at least for some patients, teachings from the study of another anti-VEGF agent, ranibizumab. *See*, Ex.1002, ¶¶204-236.

C. PO Is Not Entitled To An Earlier Priority: Grounds II-III

As set out above, the Challenged Claims are obvious over references that PO does not challenge as prior art. Thus the Board need not reach PO’s attempt to antedate the art. But should the Board reach the question, the Board should invalidate on Grounds II-III as well.⁶

⁶ Grounds VI-VIII in the Petition included the 2010 References and addressed the formulation and exclusion criteria limitations. If the Board rejects

Specifically, PO attempts to antedate 2010 ARVO Abstract and the December/November 2010 PRs based on two theories: (1) that the DA VINCI and VIEW clinical trials were conducted “on behalf of” Dr. Yancopoulos and thus inure to his benefit as reductions to practice, or (2) that the prior art “merely reflects Dr. Yancopoulos’s work.” PO has the burden as to both of these theories. *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1381 (Fed. Cir. 2015).

Both of PO’s theories fail for two fundamental, independent reasons: (1) PO failed to show Dr. Yancopoulos conceived of the invention, and (2) PO failed to show that the work was conducted “on his behalf” or reflected his sole work.

1. PO Failed to Show Dr. Yancopoulos Conceived of the Claimed Dosing Regimen

First, as to conception, “when a person relies on the activities of others to show actual reduction to practice, proof of conception is relevant to inurement.” *Sonos, Inc. v. Implicit, LLC*, No. IPR2018-00767, 2019 WL 4419356, at *6 (P.T.A.B. Sept. 16, 2019) (citing *Sensio, Inc. v. Select Brands, Inc.*, IPR2013-00580, Paper 31 at 10–15 (PTAB Feb. 9, 2015) (Final Written Decision); *Genentech, Inc. v. Chiron Corp.*, 220 F.3d 1345, 1354 (Fed. Cir. 2000)). This requirement makes sense; otherwise, a person could antedate a prior art reference without showing that

PO’s attempt to antedate, it can, but need not, include the 2010 references in the analysis of those Grounds.

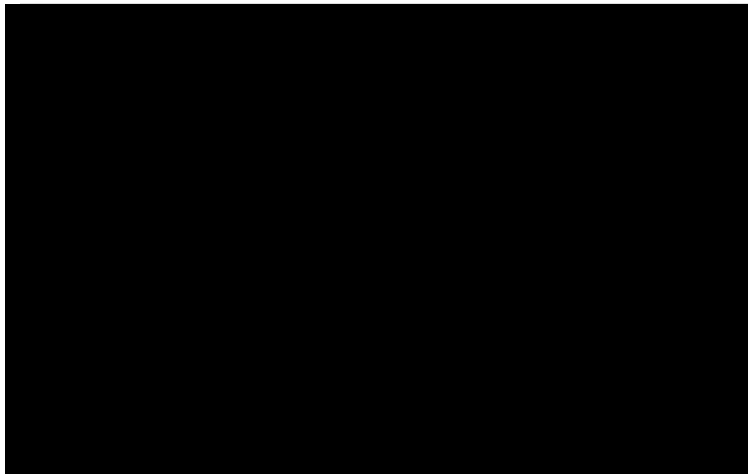
she was the first to conceive the invention, contrary to the requirements for doing so.

PO has failed to provide a corroborated conception. PO’s allegedly corroborating witness, Karen Chu, testified repeatedly that she did not recall [REDACTED] (Ex.1082, 93:10-116:12, 180:2-182:5), and more specifically that she did not know “if [REDACTED] specifically suggested [REDACTED]” including the three-loading dose/8-week maintenance regimen. Ex.1082, 116:13-23.

In fact, the first documented reference to the use of a three-loading dose/8-week maintenance regimen appears to be in an April 2, 2007 email sent by Kathleen Lawrence, a Regeneron employee. Ex.1091. In that email, she summarizes the decisions of an “AMD Phase 3 Program Mtg.” and refers to “2mg q8ks *w/PIER lead in (dose monthly for 1st 3mnths.)*.” *Id.* [REDACTED] [REDACTED]. Ex.1082, 147:4-150:25; Ex.1080, 187:9-15.

Similarly, the next reference to the relevant regimen appears in an email regarding a [REDACTED] Meeting with Bayer. [REDACTED] [REDACTED]. See Ex.2069, 8. [REDACTED] [REDACTED] Ex.1083.

PO tries to corroborate Dr. Yancopoulos’s claim to have conceived of the claimed regimen before these meetings with a single page that Dr. Yancopoulos says, without corroboration, he added to a PowerPoint presentation he allegedly attached to an email (which appears corrupted, though PO offers no explanation regarding the state of the email or alleged attachment):



Ex.2073, 9; POR, 27-29. PO points to the single highlighted line as the allegedly corroborative evidence that Dr. Yancopoulos conceived of the invention by March 22, 2007 before the emails from others summarized above.

On its face, however, this line appears to refer to [REDACTED]
[REDACTED]. It thus does not show conception of the complete invention. Dr. Yancopoulos offers uncorroborated testimony that the reference to [REDACTED]
[REDACTED] but to three loading doses of aflibercept followed by 8-week dosing. Ex.2063, ¶¶21-22. But nothing in the record corroborates this. Indeed, as set out above, in other contemporaneous documents,

Regeneron employees explicitly specified the use of loading doses when using abbreviations similar to the “[REDACTED]” abbreviation.

“It is well established... that when a party seeks to prove conception through an inventor’s testimony the party must proffer evidence, in addition to the inventor’s own statements and documents, corroborating the inventor’s testimony.” *Apator Miitors ApS v. Kamstrup A/S*, 887 F.3d 1293, 1295 (Fed. Cir. 2018) (cleaned up). PO has failed completely in its attempt to do so. In fact, outside of Dr. Yancopoulos’s say-so, the evidence of record suggests Dr. Yancopoulos was not even involved in the first meetings where the 3-loading dose/8-week regimen was discussed.⁷

2. PO Failed to Show that the Clinical Trials Were Conducted “On Dr. Yancopoulos’s Behalf” Or Reflected His Sole Work

As an independent ground for denying Patent Owner’s attempt to antedate, the challenged references themselves and other evidence definitively establish that the clinical trials were conducted as a collaboration between PO and Bayer. See Ex.1005; Ex.1006; Ex.1007; Ex.1009, 1575. Thus, even if PO’s contention that Dr.

⁷ Additionally, PO takes the position that for the efficacy claims, there was no conception until there were positive clinical trial results. Dr. Yancopoulos admitted that he did not conceive of any efficacy limitation before receiving the clinical results, further defeating Regeneron’s inurement argument. Ex.1080, 218:5-220:23; 230:2-235:3; 248:13-253:25; Ex.1082, 133:11-134:4, 158:7-165:9.

Yancopoulos played a major role in the trials was corroborated (it is not), PO has not shown why this is sufficient to prove Dr. Yancopoulos is entitled to claim the entire work of three clinical trials as his own.

In fact, the record indicates Dr. Yancopoulos did not “direct” or “control” the trials as PO alleges. As one simple example, [REDACTED] Ex.1082, 155:12-157:2. As another, [REDACTED] [REDACTED] [REDACTED] *Id.*, 158:7-18. Regeneron does nothing to explain how these acts were taken “on behalf of” Dr. Yancopoulos.

D. The Results Limitations Lack Patentable Weight: Grounds X and XI

PO does not contest Grounds X and XI other than to argue that the results limitations have patentable weight. For the reasons set out in the Petition and below, Petitioner respectfully requests the Board reconsider its decision that these limitations have patentable weight, particularly as to claim 27.

Specifically, in the ID, the Board found that the claims included some variability as to the number of doses, explaining the results thus “illuminate the dosage administration steps in a material way, i.e., so that one may know collectively how many secondary or tertiary doses are sufficient.” ID, 26-27.

Claim 27, however, recites a patient must receive a particular number of loading doses and requires treatment to week 52. *See also* cls. 5, 11. Indeed, PO’s expert acknowledged claim 27 provides no discretion as to treatment. Ex.1076, 18:3-12, 20:2-12. This distinguishes claim 27 from the claims such as in *LA Biomed v. Eli Lilly*, 849 F.3d 1049, 1061 (Fed. Cir. 2017). The results limitation in claim 27 merely happens or does not—you “get the result that you get,” as PO’s expert stated. Ex.1076, 14:13-15:5. It does not inform the rest of the claim. For that reason, at a minimum, the Board should find that claim 27’s results limitation is not entitled to patentable weight.

More broadly, even in the claims that recite “one or more secondary dose,” the results limitations do not affect and are not linked to the active steps of the method. Dr. Stewart, PO’s expert, testified that while certain claims allowed a clinician to set the loading doses, there is no discretion (i.e. “express variability,” ID, 30) in the claims allowing clinician to change the regimen in order to achieve the recited gains, nor any guidance for how to do so. Ex.1076, 18:3-24:18; 30:10-34:2. According to PO, the clinician merely measures along the way to see if the result was met; the result thus does not guide any variable of treatment (as it might in actual practice, and as it did in *LA Biomed*). *Id.* The additional results limitations lack patentable weight for this reason.

E. No Secondary Considerations

PO did not establish secondary considerations that would support a finding of non-obviousness. PO argues only one secondary consideration exists—alleged commercial success. Its showing fails.

First, there is no nexus. Nexus cannot be presumed merely because Eylea allegedly embodies the claims; PO claims Eylea embodies multiple patents to different inventions. *Cf. Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1377 (Fed. Cir. 2019); Ex.1086. Additionally, PO acknowledges the relevant dosing regimens were known in the art. But PO failed to tie the alleged commercial success to the aspects of the Challenged Claims it argues are novel—the very particular efficacy gains, which, as set out above, fall well within those already achieved with both aflibercept and ranibizumab. This failure prevents a finding of nexus.

Additionally, PO cannot establish that the claimed dosing regimen is what drives Eylea sales. For instance, PO’s expert did not analyze whether the reported Eylea sales were associated with the claimed dosing regimen, let alone apply PO’s “fixed” or “predetermined” construction in his commercial success analysis. Ex.1084, 31:19-33:12; 35:8-45:9, 79:23-100:1, 120:8-126:25; *see also* Ex.1085, 42:10-45:17, 86:13-87:5. PO’s own evidence shows the majority of the Eylea sales **were not** attributable to the claimed 8-week dosing regimen that require five initial monthly doses. Exs. 2141-2144, 2147, 2162-2199.

III. CONCLUSION

For the foregoing reasons, Petitioner requests the Board find claims 1-30 unpatentable.

DATED: June 10, 2024

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,253,572 complies with the type-volume limitation of 37 C.F.R. § 42.24 permitting a petition of up to 5,600 words because, exclusive of the exempted portions, it contains 5,596 words as counted by the word processing program used to prepare the paper.

Date: June 10, 2024

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing Reply and Exhibits 1076-1092 pursuant to 37 C.F.R. § 42.10(b) were served on June 10, 2024, to the following: Counsel for Petitioner via email to Regeneron-MoFo-IPR@mofo.com; Counsel for Biocon Biologics, Inc. at MYL_REG_IPR@rmmslegal.com; and Counsel for Celltrion, Inc. at lgreen@geminilaw.com, fchu@geminilaw.com, rcerwinski@geminilaw.com, azalcenstein@geminilaw.com, and bmorris@geminilaw.com.

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