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

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1001	U.S. Patent No. 11,253,572
1002	Expert Declaration of Dr. Edward Chaum in Support of Petition for *Inter Partes* Review of Patent No. 11,253,572, dated April 27, 2023 ("Chaum Decl.")
1003	Edward Chaum *Curriculum Vitae*
1004	Institution Decision in *Apotex Inc. v. Regeneron Pharmaceuticals, Inc.*, 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 *Apotex Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-01524 (Paper 1) ("Apotex Petition")

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1009	Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. Expert Opin Investig Drugs. 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 *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881 (Paper 94) ("'338 FWD")
1012	Institution Decision in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals*, *Inc.*, IPR2022-01225 (Paper 21) ("'681 ID")
1013	Institution Decision in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals*, *Inc.*, 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, "Opthalmic Preparations," Remington: The Science and Practice of Pharmacy, Volume II, 19th edition, Chapter 89 (1995). ("Hecht")
1017	WO 2006/047325 Al ("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

Exhibit	Description
	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-online.com/displayfilinginfo.aspx?FilingID=4380124-5423-15279&type=sect&TabIndex=2&companyid=5036&ppu=%252fdef%E2%80%A6

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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")
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")
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. 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/health-pdfs/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. 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")

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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")
1051	Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, et al, Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012; 119(7):1399-411 ("Chakravarthy 2012")
1052	Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006; 355(14):1419-31 ("Rosenfeld 2006")
1053	Heimann, H. (2007). Chapter 5 Intravitreal Injections: Techniques and Sequelae. In: Holz, F.G., Spaide, R.F. (eds) Medical Retina. Essentials in Ophthalmology. Springer, Berlin, Heidelberg. ("Heimann 2007")
1054	Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreous 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 *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, 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 *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 1:22-cv-00061-TSK, Northern District of West Virginia. (Dkt. 427) ("Mylan Litigation CC Order")
1064	U.S. Patent No. 7,531,173 ("'173 patent")

I. INTRODUCTION

Samsung Bioepis Co., Ltd. ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42 et seq., seeking cancellation of claims 1-30 (the "Challenged Claims") of U.S. Patent No. 11,253,572 ("'572 patent") (Ex.1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc.

The Challenged Claims are directed to treating angiogenic eye disorders, including diabetic macular edema ("DME") and age-related macular degeneration ("AMD"), by administering aflibercept via a number of initial monthly loading doses, followed by maintenance doses administered every two months.

One subset of the Challenged Claims—claims 15-25—is directed to a dosing regimen for DME with two or more monthly loading doses followed by maintenance doses administered every two months (the "DME Claims"). Those claims were not challenged in Apotex's prior '572 IPR Petition (IPR2002-01524 ("Apotex Petition")), which addressed the non-DME claims of the '572 patent. Ex.1008.

Unlike the other '572 claims previously addressed by the Patent Trial and Appeal Board ("Board"), independent claim 15 and dependent claim 24 recite only DME dosing regimens and nothing more. They do not contain what the Board previously referred to as a "results limitation"—i.e. maintaining or gaining visual acuity. Ex.1004, 15. Instead, claim 15 recites treating DME by administering a

single initial dose of aflibercept, followed by "one or more" monthly secondary doses (the "loading" phase), and then maintenance doses every two months. Claim 24 depends from claim 15 and recites that "only two secondary doses" are administered, meaning only three monthly doses are given before 8-week dosing.

Thus, claims 15 and 24 are anticipated by any aflibercept DME prior art disclosing three monthly loading doses followed by 8-week maintenance dosing. A Regeneron press release from September 14, 2009 ("2009 Press Release") discloses exactly that. It describes administering 2 mg aflibercept to treat DME using a dosing regimen of three monthly loading doses that include an initial and two "secondary" doses, followed by maintenance doses at 8-week intervals. Ex.1005. Another press release from December 20, 2010 ("December 2010 Press Release") discloses the same DME regimen. Ex.1006. Thus, as shown in Ground I, each of the 2009 Press Release and December 2010 Press Release anticipates claims 15 and 24.

A second subset of Challenged Claims—1-5, 8-11, 16-17, 20-21, and 26-30—recite a loading/maintenance regimen for generic angiogenic eye disorders, DME, or AMD, and also include certain "results limitations" reciting either a general result within a specific time frame (e.g., "wherein the patient achieves a gain in visual acuity within 52 [or 24] weeks") or a specific visual acuity gain (e.g., "wherein the patient gains at least 7 [or 8 or 9] letters" in the standard ETDRS letter score for

visual acuity, or wherein the regimen is "as effective" as ranibizumab). These claims are collectively referred to as the "Results Claims" herein.

Results Claims 1-5, 8-11, 16-17, and 20-21 recite treating either a generic angiogenic eye disorder or DME specifically (the "Generic Results Claims"/"DME Results Claims"). As shown in Ground II, the December 2010 Press Release anticipates the Generic/DME Results Claims. The December 2010 Press Release discloses the same dosing regimens for DME as the 2009 Press Release, but further reports the visual acuity results from DME clinical trials in which these regimens were applied. The December 2010 Press Release explicitly discloses that DME patients both achieved the results recited within the recited 24 or 52 week time frames, and that they achieved the specific visual acuity gains recited (e.g., a gain of at least 7, 8, or 9 letters).

Similarly, Results Claims 26-30 recite a method for treating AMD via a loading/maintenance regimen (the "AMD Results Claims"), and further recite that the method is "as effective" as monthly ranibizumab at week 52. As shown in Ground III, the AMD Results Claims are anticipated by a November 22, 2010 Press Release ("November 2010 Press Release"), which discloses the same dosing regimen as the other press releases, but for treatment of AMD. Ex.1007. That Press Release further explicitly discloses the ranibizumab comparison results recited by the claim. *Id*.

The Results Claims are also rendered obvious by the 2009 Press Release or separately by Dixon's disclosure of the claimed dosing regimen for AMD. Notably, in the Apotex Petition, Apotex argued that the "results limitations" only were inherent or not entitled to patentable weight based on Dixon—an argument the Board rejected; Apotex did ***not*** argue that they were obvious. Ex.1008, 12. It would have been obvious to a POSA, however, that at least some patients, when treated via the recited dosing regimens disclosed in the prior art, would achieve the recited 7-9 letter gains, which were modest compared to known gains for aflibercept. For instance, it was known that a single 2 mg dose of aflibercept produced 15 letter gains for some patients within the first six weeks of treatment. And Dixon reports that AMD patients who received four initial monthly doses, followed by PRN dosing resulting in only an average of 1.6 additional injections through 52 weeks (for a total of 5.6 doses in a year on average), achieved a mean of 9 letter gains, ***with 29% gaining at least 15 letters*** by 52 weeks. Ex.1009, Dixon, 1576.

Importantly, the Results Claims do not require every patient to achieve the recited gain. Instead, the claims are directed to methods for treating "***a*** patient," and thus a POSA only need find it obvious that some patients would achieve the recited gains. *See*, Ex.1001, claims 1, 15, 26, and 29. It would have been obvious to a POSA that at least some AMD patients would have achieved the lower 7-9 letter gains claimed in the AMD Results Claims using three initial monthly doses followed

by 8-week maintenance dosing (instead of four monthly doses followed by less frequent PRN dosing). Three initial doses followed by 8-week dosing would result in eight overall doses during the 52 week period—***two more*** doses than had been shown to produce 15 letter gains in almost 1 in 3 patients.

Similarly, as to the DME Results Claims, POSAs knew that a single initial 4 mg dose of aflibercept had produced a 9 letter gain by 4 weeks (Ex.1009, 1575) and that the DME clinical trials described in the 2009 Press Release had achieved a mean gain of "+8.5 to +11.4 letter[s]" within 24 weeks (Ex.1010, 2010 ARVO Abstract, 1).

Thus, as shown in Grounds IV and V, Dixon and the 2009 Press Release, in combination with references reporting aflibercept efficacy for AMD and DME, render obvious the Generic/AMD and DME Results Claims respectively.

Petitioner also presents Grounds VI-IX addressing various dependent claims, as further set out below. Finally, in Grounds X and XI, Petitioner addresses anticipation of the Results Claims on the basis that the "results limitations" are not entitled to patentable weight and are thus anticipated by the dosing regimens disclosed in the September 2009 Press Release and Dixon.

Discretionary denial is not appropriate here. None of the references cited in Petitioner's grounds were substantively discussed during prosecution. While Apotex previously filed a petition against the '572 patent against AMD claims

including results limitations, Apotex did not challenge any of the DME claims—including anticipated claims 15 and 24, which do not contain a "results limitation"—and Apotex did not rely on the 2009 and 2010 Press Releases as part of its grounds. *See,* Ex.1008. Moreover, Apotex did not present obviousness arguments as to the Results Claims, including as to Dixon. *Id.* The only overlap in Petitioner's grounds and Apotex's is as to minor dependent limitations and as to Grounds X and XI.

The Board should institute an *inter partes* review of the Challenged Claims and find those claims unpatentable on the grounds presented herein.

II. MANDATORY NOTICES PURSUANT TO 37 C.F.R. § 42.8(A)(1)

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest for Petitioner is Samsung Bioepis Co., Ltd.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

As noted above, Apotex filed an IPR Petition on September 9, 2022 asserting five grounds for invalidating the non-DME claims of the '572 patent, all of which recite "results limitations." Ex.1008 ("Apotex Petition"). Grounds 1-4 of Apotex's petition were based on anticipation: (1) anticipation of claims 1-5, 8-11, 14, and 26-30 based on Dixon; (2) anticipation of claims 1-5, 8-11, 14, and 26-30 based on a May 8, 2008 Regeneron Press Release; (3) anticipation of claims 1-5, 8-11, 14, and 26-30 based on NCT-795 (i.e., VIEW 1 ClinicalTrials.gov entry); and (4) anticipation of claims 1-5, 8-11, 14, and 26-30 based on NCT-377 (i.e., VIEW 2 ClinicalTrials.gov entry). Ex.1008, 12.

With respect to the "results limitations" in these claims, Apotex argued that they (1) were not entitled to patentable weight (*id*., 17-20); or (2) were inherently anticipated by practice of the claimed method (*id*., 35-68). Notably, Apotex did not rely on obviousness to address the visual acuity limitations in any of the claims.

Apotex only asserted obviousness for claims 6, 7, 12, and 13 in its Ground 5. For those claims, Apotex relied on any of the above anticipatory references in view of Hecht. Ex.1008, 12. Apotex's obviousness argument in Ground 5 was solely directed to the "isotonic solution" limitation in dependent claims 6 and 12 and the "nonionic surfactant" limitation in dependent claims 7 and 13—not the "results limitations." Ex.1008, 68-71.

In its Institution Decision, the Board determined that the "results limitations" were entitled to patentable weight. Ex.1004 ("Apotex '572 ID"), 14-18. The Board then went on to determine that the prior art did not inherently disclose the "results limitations" for at least two reasons: (1) less than all of the patients in the VIEW 1/2 trials achieved the claimed visual acuity limitations; and (2) the patient population reported in the prior art as achieving the recited gains was not the same as that described in the '572 patent. *Id*, 30-36. It therefore denied institution. *Id.*

The '572 patent is in the same family as U.S. Patent Nos. 9,254,338 ("'338 patent"), 9,669,069 ("'069 patent"), 10,130,681 ("'681 patent"), and 10,888,601 ("'601 patent"). Ex.1001.

In May 2021, Mylan Pharmaceuticals Inc. filed petitions requesting *inter partes* review of the ’338 and ’069 patents. *See* IPR2021-00881 (“’338 IPR”) and IPR2021-00880 (“’069 IPR”). The Board instituted review for the ’338 and ’069 patents and found all challenged claims of those patents unpatentable in Final Written Decisions issued on November 9, 2022. *See* Ex.1011, ’338 IPR, Paper 94 (“’338 FWD”); ’069 IPR, Paper 89.

Mylan filed a petition requesting IPR of the ’681 patent on July 1, 2022 (IPR2022-01225) (“Mylan ’681 IPR”). The Mylan ’681 IPR was instituted on January 11, 2023. Ex.1012 (“’681 ID”). Petitioner filed a petition against the ’681 patent on January 6, 2023 (IPR2023-00442) asserting different grounds of invalidity than in the Mylan ’681 IPR. A decision on Petitioner’s petition is pending.

Mylan filed a petition requesting IPR of the non-DME claims of the ’601 patent on July 1, 2022. *See* IPR2022-01226 (“Mylan ’601 IPR”). The Mylan 601 IPR was instituted on January 11, 2023. Ex.1013 (’601 ID). Petitioner filed a “copycat” IPR petition on February 10, 2023. *See, Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00566, Papers 2-3. The Board instituted Petitioner’s IPR petition and granted its motion for joinder on March 22, 2023 in IPR2023-00566. *Id.*, Paper 10.

Petitioner filed a petition requesting IPR of the DME claims of the ’601 patent on March 26, 2023. *See Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00739. A decision on Petitioner’s petition is pending.

To the best of Petitioner’s knowledge, the following are judicial or administrative matters that potentially would affect, or be affected by, a decision in this proceeding: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, NDWV-1-22-cv-00061 (“Mylan Litigation”), *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.).

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)-(4)

Petitioner hereby identifies its lead and backup counsel as follows:

Lead Counsel	Backup Counsel
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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please send all correspondence to the lead and backup counsel at the addresses shown above. Petitioner consents to service by e-mail at qe-samsungbioepis@quinnemanuel.com.

E. Payment of Fees (37 C.F.R. §§ 42.103 and 42.15(a))

The requisite filing fee of $52,750 (request fee of $22,750, post-institution fee of $30,000) for a Petition for *Inter Partes* Review is submitted herewith. Claims 1-30 are being reviewed as part of this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No.

505708. Any overpayment or refund of fees may also be deposited in this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a); 37 C.F.R. §§ 42.101(a)-(c))

Petitioner certifies that the ’572 patent is available for IPR and that Petitioner is not barred or estopped from requesting this review.

IV. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

A. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of ’572 patent claims 1-30 and that the Board cancel those claims as unpatentable.

B. Grounds of Challenge (37 C.F.R. § 42.204(b)(2))

Petitioner respectfully requests that the Board grant institution of IPR on the Challenged Claims based on the following grounds:

Statutory Grounds of Challenge	
Ground I	Claims 15 and 24 are anticipated by each of the 2009 Press Release and December 2010 Press Release
Ground II	Claims 1-5, 8-11, 16-17, and 20-21 are anticipated by the December 2010 Press Release

Ground III	Claims 26-30 are anticipated by the November 2010 Press Release
Ground IV	Claims 1-5, 8-11, and 26-30 are rendered obvious by Dixon alone or in view of the 2006 Press Release
Ground V	Claims 16-17, and 20-21 are rendered obvious by the 2009 Press Release alone or in view of the 2007 ARVO Abstract, Dixon and/or the 2010 ARVO Abstract (collectively "Ground V References")
Ground VI	Claims 6-7 and 12-13 are rendered obvious by each of Dixon in view of Hecht, Dixon in view of the 2006 Press Release and Hecht, and the December 2010 Press Release in view of Hecht
Ground VII	Claims 18-19 and 22-23 are rendered obvious by each of the December 2010 Press Release in view of Hecht, and the 2009 Press Release in view of the Ground V References and Hecht
Ground VIII	Claim 14 is rendered obvious by each of Dixon and the December 2010 Press Release alone or in view of the CATT Study and/or PIER Study

Ground IX	Claim 25 is rendered obvious by the 2009 Press Release alone or in view of Shams or Elman 2010
Ground X	Claims 1-5, 8-11, and 26-30 are anticipated by Dixon because the "results limitations" lack patentable weight
Ground XI	Claims 1-5, 8-11, 16-17, and 20-21 are anticipated by the 2009 Press Release because the "results limitations" lack patentable weight

V. THE '572 PATENT

A. Overview

The '572 patent issued on February 22, 2022. The '572 patent names as its sole inventor, George D. Yancopoulos. Ex.1001; *see generally,* Ex.1002, ¶¶70-73.

The '572 patent specification discloses that "the methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist" to treat angiogenic eye disorders, i.e., eye disorders caused by or associated with the formation of new blood vessels. Ex.1001, Abstract; 1:30-56.

Examples 1-6 of the '572 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.,* Cols. 7-17.

Example 7 of the ’572 patent describes additional dosing regimens, but does not contain any test results. *Id.,* 15:35-17:28.

B. Priority Date

Claim 25 recites the use of five loading 2mg doses to treat DME, followed by 8 week maintenance dosing. That dosing regimen—including the recited dosage (2.0 mg), the recited interval between secondary doses and tertiary doses (4 weeks and 8 weeks, respectively), the recited indication (DME), or a combination of those variables for the treatment of DME/DR—was not described in the specification of any application to which the ’572 patent claims priority prior to July 12, 2013. Ex.1002, ¶¶91-103.

Based on at least the priority date of claim 25, AIA Sections 102 and 103 apply to the prior art discussed in this petition (*see* MPEP §2159), but even if pre-AIA Sections 102 and 103 apply, Petitioner’s arguments are the same.[1] Petitioner reserves all rights to challenge the extent to which Regeneron asserts application of pre-AIA standards of patentability.

[1] For the purposes of this petition only, Petitioner assumes a priority date of January 21, 2011 for the other claims.

C. The Challenged Claims

Independent claims 1, 15, 26, and 29 are directed to methods for treating an angiogenic eye disorder, age-related macular degeneration, or diabetic macular edema in a patient by administering a single initial dose of 2mg of aflibercept, followed by one or more secondary doses 4 weeks apart, and one or more tertiary doses 8 weeks apart. Ex.1001; *see generally*, Ex.1002, ¶78-79. Notably, the independent claims recite methods for treating "***a*** patient in need thereof," not an entire patient population or a percentage thereof, because that is all the specification describes. These claims do not recite efficacy for a broader population or recite that the regimen be more efficacious than other regimens. Ex.1001.

The four independent claims differ in their recitation, if any, of "results limitations" and indications. Ex.1001; *see generally,* Ex.1002, ¶¶78-79. Claim 15 is directed to treating DME and does not recite any results limitation. Claim 1 is directed to any angiogenic eye disorder and recites a gain in visual acuity within 52 weeks after the initial dose. *Id.* Claims 26 and 29 are directed to AMD and recite that the method be as effective as monthly administration of 0.5 mg of ranibizumab by intravitreal injection at 52 weeks following the initial dose. *Id.*

Dependent claims 2-5, 8-11, 16-17, 20-21, 24, and 27-28 and 30 further specify the number of secondary doses, gains in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter

score, and weeks to achieve the efficacy results. *Id.* Dependent claims 6-7, 12-13, 18-19 and 22-23 recite that the aflibercept is formulated as an isotonic solution or with a nonionic surfactant. Dependent claim 14 recites two exclusion criteria. *Id.* Claim 25 recites that the number of initial loading doses for treating DME is five total. *Id* .

D. Prosecution History

The ’572 patent issued from U.S. Application No. 17/352,892, filed on June 21, 2021. Ex.1014, ’572 patent PH. Ex.1014; *see also,* Ex.1002, ¶¶74-77. On October 28, 2021, the Examiner issued a non-final office action rejecting the pending claims on the ground of non-statutory obviousness-type double patenting as being unpatentable over certain claims of the ’338, ’069, ’681, ’345, and ’601 patents. Ex.1014, 1239-1245. In response, the applicants submitted terminal disclaimers to the reference patents. *Id.*, 1315-1319. On December 22, 2021, the Examiner issued a notice of allowance for the claims without making a further rejection over prior art disclosing the same dosing regimen as the reference patents. *Id.,* 1334-1340.

E. Level of Ordinary Skill in the Art

The ’572, ’338, and ’601 patents are in the same family with the same specification. In the Mylan ’338 and ’601 IPRs, the petitioner proposed the following definition for the relevant person of ordinary skill in the art:

> A person of ordinary skill in the art at the time of the invention would have had (1) knowledge regarding the

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

Ex.1011, '338 FWD, 9-10; Ex.1013, 15-16. In the '601 ID and '338 FWD, the Board found that this definition was consistent with the proper level of skill. Ex.1013, 15-16; Ex.1011, 10; *see also* Ex.1012, '681 ID, 20-21. The Board further accepted this definition in ruling on Apotex's '572 Petition. Ex.1004, 11. Petitioner proposes the same definition be adopted here. *See also* Ex.1002, ¶¶22-25.

VI. CONSTRUCTION OF THE CHALLENGED CLAIMS

A. "A method of treating…"

For the purposes of this petition only, Petitioner does not contest that the preamble of challenged claims 1, 15, 26, or 29 is limiting, though it reserves the right to do so in separate proceedings. Petitioner proposes that the preamble be given the

meaning of "a method for treating…" consistent with the meaning given to that term in the '338 FWD and '601 ID. Ex.1011; Ex.1013. Petitioner further proposes that the claims not be construed to require a particular level of efficacy.

Specifically, in the '338 FWD, '601 ID, and '681 ID, the Board found that administering a compound—the recited VEGF antagonist—"to [a] patient ***for the purpose*** of improving or providing a beneficial effect on their angiogenic eye disorder" satisfies the "treating" portion of the preamble. Ex.1011, 19 & 23; Ex.1013, 9-10; Ex.1012, 10-12.

For purposes of this proceeding, Petitioner agrees with that understanding of the term as it appears in the preamble here. *See also* Ex.1002, ¶¶26-30, 80-85; Ex.1001, 5:31-48; claims 1, 8, 17, 21, and 30 (claiming both loss and gain of visual acuity). Administration of aflibercept to a patient for the ***purpose*** of treating them the recited disorders using the recited dosing regimen is sufficient to effectively "treat." *Id.*

B. Exclusion Criteria

Dependent claim 14 recites two exclusion criteria.

In the '601 ID, the Board found that the same exclusion criteria recited here are not entitled to patentable weight. Ex.1013, 12-15; *see also* Ex.1012, 18-20. Relying on the two-step test in *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018), the Board found that "there is little

question that the exclusion criteria are directed to informational content" under the first step of the *Praxair* analysis. The Board further found that under the second *Praxair* step, the exclusion criteria lacked a functional relationship to the rest of the claims, particularly because "the claims do not expressly recite any positive step to be performed (or negative step *not* to be performed) should a patient meet the exclusion criteria." Ex.1013, 14; *see also* Ex.1012, 19.

In its April 19, 2023 claim construction order, the district court in the Mylan Litigation likewise found the recited exclusion criteria as lacking patentable weight. Ex.1063, 29-37. The court found that the recited exclusion criteria "do[] not ***require*** any action step to be taken as a consequence of" assessing a patient for the recited inflammation or infection. *Id.* 34-35 (emphasis original). In other words, "nothing [about recited the exclusion criteria] has transformed the process of taking the drug aflibercept in the claimed method – the actual method …[with] 2mg of aflibercept, on the stated dosing schedule, remains the same." *Id.* And, the exclusion criteria are simply "a non-binding informational 'option' for doctors to consider." *Id.* Since there is no additional step that "flows from" the exclusion criteria, the court concluded that the exclusion criteria are not entitled to patentable weight. *Id.*

Petitioner agrees with the understanding of the Board and the district court. The same exclusion criteria are not entitled to patentable weight in the Challenged Claims. *See also* Ex.1002, ¶¶26-30; 86-90.[2]

VII. SCOPE AND CONTENT OF THE PRIOR ART

Petitioner summarizes the scope and content of the prior art, including the disclosures of its primary prior art references, below. As discussed in Section V.B, AIA 35 U.S.C. §102 applies to the '572 patent. However, all references discussed herein are prior art under both pre-AIA and AIA U.S.C. §102 and Petitioner's arguments are the same.

A. The 2009 Press Release

The 2009 Press Release was published on September 14, 2009, and thus constitutes prior art under both pre-AIA and AIA 35 U.S.C. § 102. Ex.1005. It reflects its date on its face, was submitted during prosecution, but was never substantively addressed by the Examiner.

The 2009 Press Release discusses VEGF Trap-Eye, also known as aflibercept. Ex.1005; *see also, e.g.*, Ex.1015; Ex.1009. It discusses a number of clinical trials for various indications of VEGF Trap-Eye, including AMD and DME. *Id.* As to

[2] Petitioner separately addresses the patentable weight of the "results limitations" in Grounds X and XI below.

DME, the press release specifically states that VEGF Trap-Eye is "in Phase 2 development for the treatment of Diabetic Macular Edema (DME)." Ex.1005, 1. It teaches that the trial an arm consisting of 2mg VEGF Trap-Eye administered via three monthly loading doses followed by dosing every eight weeks. *Id.*; *see also*, Ex.1002, ¶¶104-105.

B. The November 2010 Press Release

The November 2010 Press Release was published on November 22, 2010, and thus constitutes prior art under both pre-AIA and AIA 35 U.S.C. §102. Ex.1007. It reflects its date on its face and was never substantively addressed by the Examiner.

The November 2010 Press Release discloses the results of VEGF Trap-Eye administered via three monthly loading doses followed by dosing every eight weeks, including a summary of the efficacy data showing mean improvements in vision of 7.9 and 8.9 letters at 52 weeks versus baseline. *Id.*, 4; Ex.1002, ¶¶106-107.

C. The December 2010 Press Release

The December 2010 Press Release was published on December 20, 2010, and thus constitutes prior art under both pre-AIA and AIA 35 U.S.C. §102. Ex.1006. It reflects its date on its face and was never substantively addressed by the Examiner.

The December 2010 Press Release discloses the results of the Phase II DA VINCI study for the treatment of DME with aflibercept. Ex.1006; *see also*, Ex.1002, ¶¶108-109. It discloses that the DA VINCI study included a study arm with three

initial monthly doses of 2mg aflibercept followed by either dosing every two months or PRN (as-needed) dosing through week 52. Ex.1006, 1-2. It also includes efficacy data showing mean changes in visual acuity of 8.5 and 9.7 letters at weeks 24 and 52 respectively in the dosing arm with bimonthly doses following three initial monthly doses. *Id.,* 2-3.

D. Dixon

Dixon et al., "VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration," Expert Opn. Investig. Drugs, 18(10): 1573-80 (2009)) ("Dixon") is a peer reviewed publication describing, *inter alia*, the Regeneron Phase III clinical trials known as VIEW 1 and VIEW 2. Ex.1009. Dixon was published in 2009, and thus constitutes prior art under both pre-AIA and AIA 35 U.S.C. § 102. *Id.*

Dixon reviews clinical trial data regarding administering aflibercept to treat neovascular AMD. *Id.* 1573; *see also,* Ex.1002, ¶¶110-113. Dixon discloses that "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." Ex.1009, 1573. Dixon discloses that in a Phase II trial, AMD patients who received four initial monthly doses, followed by only an average of 1.6 additional injections through 52 weeks (for a total of ~5.6 doses in a year on average), achieved a mean of 9 letter gains, with 29% gaining greater than 15 letters, by 52 weeks. *Id.,* 1576.

Dixon further describes VEGF Trap-Eye as "a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment." Ex.1009, 1575. Dixon also discloses that "VEGF Trap-Eye and aflibercept (the oncology product) have ***the same molecular structure***, but there are substantial differences between the preparation of the purified drug product and their formulations." *Id.* (emphasis added).

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

E. Hecht

Hecht, a chapter in *Remington: The Science and Practice of Pharmacy*, Volume II, was published in 1995, and thus constitutes prior art under both pre-AIA and AIA 35 U.S.C. § 102. Ex.1016. Hecht reflects its date on its face and was never substantively addressed by the Examiner. Hecht provides guidance on formulating ophthalmic solutions for injection. *Id.*; *see also* Ex.1002, ¶¶114-115.

F. Shams

Shams is a Genentech patent application, titled "Method for treating intraocular neovascular diseases," and generally relates to methods for treating an

intraocular neovascular disorder with a VEGF antagonist. Ex.1017. Shams published in 2006 and is prior art under both pre-AIA and AIA 35 U.S.C. § 102. *Id.* Shams teaches loading and maintenance dosing, and further that the time for each dose can be modified through "routine adjustments to the dosing schedule." *Id.*; *see also*, Ex.1002, ¶¶116-118.

G. Elman 2010

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") is prior art under both pre-AIA and AIA 35 U.S.C. § 102.[3] Ex.1018; Ex.1019. It was not cited during the prosecution. Ex.1014.

Elman 2010 describes a Phase III trial for ranibizumab for the treatment of DME. Ex.1018; *see also* Ex.1002, ¶¶119-126. In the Elman 2010 trial, one of the subject groups was given four initial monthly loading doses. After the four loading

[3] Elman 2010 reflects a publication date of April 27, 2010, with a 2010 copyright. Ex.1018, 1077 ([a]vailable online: April 27, 2010"). The entry in Ophthalmology lists its online publication date as April 27, 2010, with publication in Volume 117, Issue 6 in June 2010. Ex.1019, https://www.aaojournal.org/article/S0161-6420(10)00243-5/fulltext.

doses were given, a clinician evaluated the subjects a month later to determine if a fifth monthly dose should be given. *Id.* Elman 2010 reports that at least 78% of patients received a fifth loading monthly dose. *Id.,* 1067.

H. CATT and PIER Studies

Claim 14 of the '572 patent recites two exclusion criteria for "(1) active intraocular inflammation" and "(2) active ocular or periocular infection." Ex.1001.

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	
"(1) ***active intraocular inflammation***" – i.e. current inflammation within the eye	"***Active*** or recent (within 4 weeks) ***intraocular inflammation*** (grade trace or above) in the study eye." Ex.1020, CATT Study, 6-7. "***Active intraocular inflammation*** (grade trace or above) in the study eye." Ex.1021, 248.e3.
"(2) ***active ocular or periocular infection***" – i.e. a current infection anywhere on/in the eye (ocular) or surrounding it within its orbit (periocular)	"***Active*** infectious conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***." Ex.1020, 6-7. "***Infectious*** conjunctivitis, keratitis, scleritis, or endophthalmitis ***in either eye***." Ex.1021, 248.e3.

See also, Ex.1002, ¶¶127-134. These references were not considered during prosecution of the '572 patent. Ex.1014.

The University of Pennsylvania sponsored the CATT study, which evaluated bevacizumab and ranibizumab. *See* Ex.1022, NCT00593450; *see also,* Ex.1002, ¶129-131. The web archive of its website provides a document (the "CATT Study") listing exclusion criteria for CATT as of July 13, 2010. Ex.1020; Ex.1002, ¶130. Thus, the CATT Study is prior art to the '572 patent under both pre-AIA and AIA 35 U.S.C. § 102. *See also* Ex.1020, 1-2 (showing public availability).

The PIER study (NCT00090623) evaluated the efficacy and safety of ranibizumab (Lucentis®) administered monthly for three months and then quarterly. Ex.1021; Ex.1002, ¶¶132-134. 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) ("PIER Study"), published February 2008, describes the PIER study and is prior art to the '572 patent under both pre-AIA and AIA § 102. *Id.*; *see also* Ex.1023-1026 (showing public availability).

I. Prior Art Regarding Aflibercept Efficacy

In addition to the art discussed above, a POSA would have been aware of the results of various Phase I and Phase II trials for AMD and DME for aflibercept from additional references. *See* Ex.1002, ¶¶135-138. For instance, a Regeneron May 1, 2006 Press Release ("2006 Press Release") discloses a six-week Phase I trial of VEGF Trap-Eye involving a "single intravitreal injection of 0.05, 0.15, 0.5, 1, 2, or

4 milligrams (mg) of VEGF Trap" for treatment of AMD. Ex.1027. It reports that at six weeks—i.e. well within the 24 or 52 week timepoints in the patent—"the two highest dose groups (2 mg and 4 mg) [showed] the mean improvement in BCVA [] 13.5 letters, with three of six patients gaining 15 or more letters." *Id*., 2; *see also* Ex.1028, Nguyen 2009, at Fig. 3B (showing 14 letter ETDRS gain by Day 15 for 2.0/4.0mg). The results were reported at the ARVO annual meeting and made available on Regeneron's website. *Id*., 1; *see also* Ex.1028, Nyugen 2009 (further reporting results, confirming letter score measured by ETDRS).

Similarly, a Regeneron May 8, 2008 Press Release ("2008 Press Release") describes the Phase II clinical trial data concerning VEGF Trap-Eye for AMD, which "met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart)." Ex.1029¸ 1-2. It reports that "[r]esults from the Phase II study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision." *Id.* Dixon further reports on these results, noting that they suggest aflibercept is at least as promising as ranibizumab, and referring to aflibercept as the "most promising anti-VEGF investigational drug." Ex.1009, 1577.

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

The Phase II results for aflibercept for DME were then reported at the ARVO Annual Meeting in April, 2010 ("2010 ARVO Abstract"). Ex.1010. In this trial, aflibercept was "dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2 mg on an as-needed (PRN) basis after three monthly loading doses" through 6 months. Ex.1005, 1. It was reported at the ARVO Annual Meeting that "[a]t 6 months [24 weeks], the mean change in BCVA for each VTE arm ranged from +8.5 to +11.4 letters" and that "[n]o significant difference was noted among the VTE arms." Ex.1010.

VIII. DETAILED GROUNDS FOR INVALIDITY

A. Ground I: Claims 15 and 24 Are Anticipated by Each of the 2009 Press Release and December 2010 Press Release

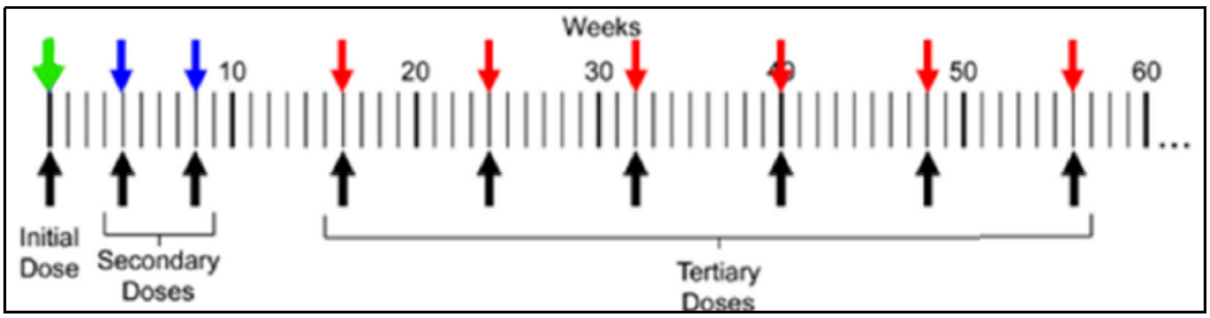
The 2009 Press Release and December 2010 Press Release each anticipate claims 15 and 24 of the '572 patent. *See* Ex.1002, ¶¶139-144.

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

The 2009 Press Release discloses treating DME with three initial loading doses and then maintenance doses every 8 weeks. It states that "VEGF Trap-Eye is… in Phase 2 development for the treatment of Diabetic Macular Edema (DME). VEGF-Trap dosed at…***2 mg every eight weeks after three monthly loading doses***…is being compared to focal laser treatment." Ex.1005, 1. Likewise, the December 2010 Press Release discloses the study design and results of the same Phase II clinical trial of aflibercept and states that one of the treatment arms included "patients with clinically significant DME … receiv[ing] ***three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by … every two months dosing***..." Ex.1006, 2.

As further illustrated in the annotated version of the sole figure of the '572 patent, the 2009 Press Release and December 2010 Press Release disclose an initial

dose (green), followed by two secondary doses (blue) (for a total of "three monthly doses"), further followed by tertiary doses (red) given "every eight weeks" or "every two months" through week 52:



Ex.1002, ¶142. This is precisely the dosing regimen recited by claims 15 and 24—an initial dose at baseline and two secondary doses at weeks 4 and 8, followed by tertiary doses every 8 weeks. *Id.*

Moreover, the Phase II dosing regimen disclosed in the 2009 Press Release and December 2010 Press Release was a method of "treating" patients with DME—i.e. it was "for the purpose" of treating DME. Ex.1002, ¶143-144. In other words, based on its use in a Phase II trial to confirm efficacy and on past results successfully treating DME, the administration of aflibercept according to the Phase II dosing regimen disclosed in the 2009 Press Release and December 2010 Press Release was ***for the purpose*** of improving or providing a beneficial effect.[4] *Id.*

[4] *See also* Exs.1011-13.

Further, consistent with the Board's prior findings that VEGF Trap-Eye and aflibercept were synonyms for the same drug, the use of VEGF Trap-Eye disclosed in the 2009 Press Release and December 2010 Press Release inherently and necessarily disclosed the use of aflibercept.[5] *See,* Exs.1011-13; Ex.1002, ¶143.

For the forgoing reasons, each of the 2009 Press Release and December 2010 Press Release anticipates every element of claims 15 and 24. Ex.1002, ¶139-144.

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

Claims 1-5, 8-11, 16-17, and 20-21, the "generic/DME Results Claims," recite the same dosing regimen as claim 15 and require certain visual acuity gains. As discussed in Ground I, the December 2010 Press Release discloses the recited

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[5] It was understood and known at the time that VEGF Trap-Eye and aflibercept were the same drug, and the protein's structure is inherent in it. For instance, Dixon expressly teaches that aflibercept and VEGF Trap-Eye have the "same molecular ***structure***" (Ex.1009, 3), and Adis (Ex.1015) refers to them interchangeably. *See also* Ex.1011, '338 FWD, 34; Exs.1035-37; Ex.1002, ¶¶50-57. Additionally, Patent Owner has repeatedly indicated to the Patent Office that they are the same drug. *Compare* Ex.1038, 3-5 (describing VIEW 1/2) with Ex.1009, 1576 (describing same); *see also* Ex.1011, '338 FWD (reviewing Patent Owner's admissions).

dosing regimen. The December 2010 Press Release further reports the visual acuity gain results from a Phase II DME clinical trial and anticipates all elements of the generic/DME Results Claims. *See* Ex.1002, ¶¶145-153.

1. Claims 1 and 16

Independent claim 1 and dependent claim 16 require the same loading and maintenance dosing regimen of claim 15, other than the identification of the disease to be treated (generic angiogenic eye disorder in claim 1 v. DME claim 16), and additionally recite "the patient achieves a gain in visual acuity within 52 weeks following the initial dose." The December 2010 Press Release reports that "[i]n Phase 2 study in DME, patients in all VEGF Trap-Eye Dose groups, including VEGF Trap-Eye dosed every two months, [following three monthly doses], ***maintained or increased vision gains through 52 weeks***." Ex.1006, 1. Specifically, a mean gain of 9.7 letters was achieved by week 52 for the "patients with clinically significant DME … [who] received three initial monthly doses of 2mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 52 by … every two months dosing…" as shown below:

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

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

Ex.1006, 3.

Accordingly, claims 1 and 16 are anticipated by the December 2010 Press Release. *See* Ex.1002, ¶¶147-148.

2. Claim 2

Claim 2 depends from claim 1 and recites that "the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." As set out in claim 1, the December 2010 Press Release discloses that patients achieved a gain in letters scores that a POSA would have understood were in BCVA according to ETDRS score, given that the December 2010 Press Release describes ETDRS as the "standard chart used in research to measure visual acuity." Ex.1006, 3; *see also*, Ex.1002, ¶¶149-150.

3. Claims 3, 8, 10, 17, and 21 and Claims 4, 9, and 20

Claims 3, 8, 10, 17, and 21 depend from claims 2 and 16 and additionally require that "the patient gains at least [7, 8, or 9] letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" within 52 weeks. Claims 4, 9, and 20 require the gain within 24 weeks. As

discussed in Section VII.B, the December 2010 Press Release reports that a *mean* gain of 9.7 letters was achieved by week 52. Ex.1006, 2-3. The December 2010 Press Release also reports that a mean gain of 8.5 letters was achieved by week 24:

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

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

Ex.1006, 3; *see also* Ex.1031, Do 2011, Figure 3.

A POSA would have understood that the reported *mean* gain of 8.5 letters necessarily indicated that there were at least ***some*** patients who had a gain in visual acuity of at least 9 letters, given letters scores are measured in whole letters and the mean is the average of these scores. Ex.1002, ¶152. Accordingly, the December 2010 Press Release anticipates claims 3, 8, 10, 17, and 21 and claims 4, 9, and 20. *See Id.*, ¶¶151-153.

4. Claims 5 and 11

Claim 5 and 11 depend from claims 3 and 10 respectively and additionally recite that "only two secondary doses are administered to the patient." As discussed in Section VIII.B.3, the December 2010 Press Release anticipates claims 3 and 10, and the additional limitation of "two secondary doses" is disclosed in the December

2010 Press Release as part of the regimen's use of three initial monthly doses. *See* Ex.1002, ¶¶153.

C. Ground III: Claims 26-30 (AMD Results Claims) Are Anticipated by the November 2010 Press Release

Claims 26-30, the "AMD Results Claims," recite the same loading and maintenance doses of claim 15, but differ with respect to the identification of the disease to be treated (e.g., AMD v. DME) and the efficacy limitations requiring the methods to be "as effective" as monthly administration of ranibizumab. The November 2010 Press Release discloses the Phase III AMD trial design of aflibercept along with the associated efficacy results and anticipates claims 26-30. *See*, Ex.1002, ¶¶154-161.

1. Claims 26-28

Claim 26 recites the same dosing regimen as claims 1 and 15, but further recites that the claimed method is "as effective in achieving a gain in visual acuity" as monthly administration of 0.5 of ranibizumab in AMD patients "at 52 weeks." Dependent claim 27 specifies that only two secondary doses are given, as disclosed in the November 2010 Press Release. Ex.1007, 3-4; *see also* Section VII.C. Dependent claim 28 recites the gain is measured using ETDRS, as also disclosed in the November 2010 Press Release. *Id.,* 4, table reproduced below.

The November 2010 Press Release discloses Phase III AMD clinical trials of aflibercept in which "VEGF Trap-Eye was evaluated for its effect on maintaining

and improving vision when dosed as an intravitreal injection on a schedule of … ***2mg every two months (following three monthly loading doses),*** as compared with intravitreal ranibizumab administered 0.5 mg every month during the first year of the studies."[6] Ex.1007, 3. This is exactly the dosing regimen recited by claims 26-28. *See* Ex.1002, ¶¶155-159; *see also,* Ground I.

As to the "results limitation," for the purposes of this petition only, Petitioner assumes that monthly ranibizumab produces a mean gain of visual acuity between 8.1-9.4 letters as reported in Table 1 of the '572 patent (Ex.1001, 13:5-40).[7] The November 2010 Press Release reports a mean improvement/gain in visual acuity between 7.9 and 8.9 letters for patients receiving bimonthly doses of 2 mg aflibercept after three initial monthly doses at Week 52, which it identifies as statistically non-inferior to monthly ranibizumab. Ex.1007, 4. Notably, these are the same values as reported in Table 1 of the '572 patent, which also identifies these results as non-significantly different than the reported ranibizumab results. Ex.1001, col 13:5-35. The November 2010 Press Release summarizes the efficacy results as shown below:

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[6] As noted above in fn. 4, it was understood at the time that VEGF Trap-Eye and aflibercept were the same drug.

[7] Petitioner reserves the right to challenge this "results limitation" as indefinite.

	Ranibizumab 0.5mg monthly	VEGF Trap-Eye 0.5mg monthly	VEGF Trap-Eye 2mg monthly	VEGF Trap-Eye 2mg every 2 months
Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline				
VIEW 1	94.4%	95.9%**	95.1%**	95.1%**
VIEW 2	94.4%	96.3%**	95.6%**	95.6%**
Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value versus ranibizumab 0.5mg monthly)* **				
VIEW 1	8.1	6.9 (NS)	10.9 (p<0.01)	7.9 (NS)
VIEW 2	9.4	9.7 (NS)	7.6 (NS)	8.9 (NS)

* Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart

** Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for VIEW 1 and VIEW 2, respectively)

*** Test for superiority

NS=non-significant

Ex.1007, 4; *id*. at 1 ("VEGF Trap-Eye dosed every two months [after three monthly doses], ***successfully met the primary endpoint compared to the current standard of care, ranibizumab dosed every month***. The primary endpoint was statistical non-inferiority in…patients who ***maintained (or improved) vision over 52 weeks compared to ranibizumab***.") Ex.1007, 1.

Given its use in a Phase III trial to confirm efficacy for regulatory approval and a number of successful past clinical trials, the administration of aflibercept according to the November 2010 Press Release was a method of "treating" patients with AMD as the term was understood by a POSA. Accordingly, the November 2010 Press Release anticipates claims 26-28. *See*, 1002, ¶¶155-159.

2. Claims 29-30

Claim 29 recites the same dosing regimen as claims 1, 15, and 26 but further recites that the claimed method is "as effective in maintaining visual acuity" as monthly administration of 0.5 of ranibizumab in AMD patients "at 52 weeks." The

claims refer to "***a*** patient," and the patent does not disclose what it means to be "as effective" as monthly ranibizumab for an individual patient. For the purposes of this petition only, Petitioner assumes that monthly ranibizumab produces a gain of visual acuity between 8.1-9.4 letters and prevents a loss of more than 15 letters, which is the result reported in Table 1 of the '572 patent. Ex.1001, 13:5-35. Claim 30 further specifies that such maintenance "means loss of less than 15 letters" BCVA as measured by ETDRS. Accordingly, the November 2010 Press Release only need to disclose that its dosing regimen prevented loss of more than 15 letters BCVA in ***some*** patients in order to be "as effective in maintaining visual acuity" as monthly ranibizumab at 52 weeks.

The November 2010 Press Release states that "[m]aintenance of vision was defined as losing fewer than three lines (equivalent to 15 letters) on the ETDRS eye chart" in the Phase III AMD trial, and that maintenance was achieved. *Id*., 2. Specifically, the November 2010 Press Release reports that 95.1-95.6% of patients who received bimonthly doses of 2mg aflibercept followed by three initial monthly doses achieved maintenance of vision at week 52, which is comparable to 94.2% reported for the monthly ranibizumab arm. Moreover, as noted above, the claimed dosing regimen disclosed in the November 2010 Press Release not only maintained visual acuity, but also produced additional visual acuity gains that were comparable to those of the monthly ranibizumab arm. Therefore, the recited dosing regimen

disclosed in the November 2010 Press Release was "as effective in maintaining visual acuity" as the monthly ranibizumab. The November 2010 Press Release anticipates claims 29-30. *See,* Ex.1002, ¶¶160-161.

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

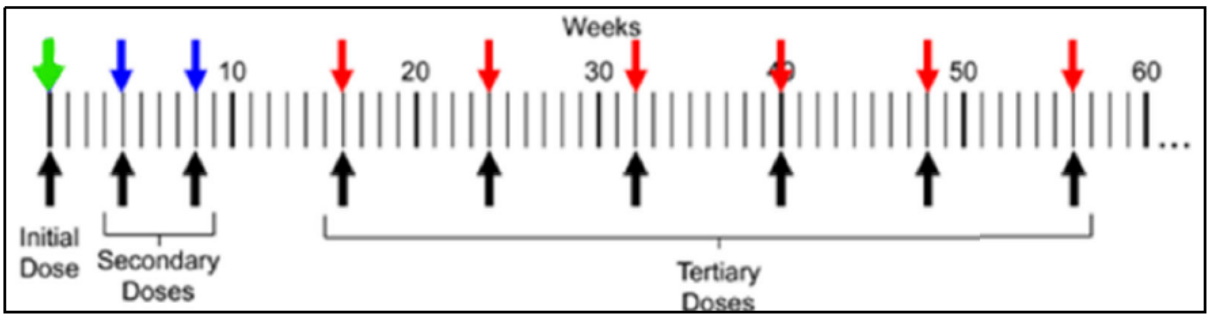
Dixon discloses all of the limitations of independent claims 1, 26, and 29, other than the "results limitations." Ex.1002, ¶¶162-165.

Dixon teaches administering the recited dosing regimen to a patient for the purpose of treating an angiogenic eye disorder, including AMD. Ex.1009; Ex.1002, ¶163. Dixon teaches that "VEGF Trap-Eye is a novel anti-VEGF drug currently in commercial development ***for the treatment*** of neovascular AMD by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA)…." Ex.1009, 1573, 1575-77 (emphasis added); *see generally* Ex.1002, ¶162-165.

As to the specific dosing regimen, Dixon discloses that the Phase III study "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of… ***2.0 mg at an 8 week dosing interval*** (***following three monthly doses***)…." Ex.1009, 1576 (emphasis added).[8] As shown below in an annotated version of the sole '572

[8] Dixon expressly teaches that aflibercept and VEGF Trap-Eye have the "same molecular ***structure***." Ex.1009, 1575. *See also* fn. 4, *supra*.

Figure, Dixon discloses an initial dose (green), followed by two secondary doses (blue) (for a total of "three monthly doses"), further followed by tertiary doses (red) given at an "8 week dosing interval":



While Dixon does not expressly disclose the "results limitations" in independent claims 1, 26, or 29 or their dependents, it renders them obvious alone or in view of the knowledge of a POSA regarding aflibercept efficacy, as discussed below. *See* Ex.1002, ¶¶162-165.

1. Claim 1

Independent claim 1 recites that "the patient achieves a gain in visual acuity within 52 weeks following the initial dose." Notably, for claim 1 and all of the Results Claims other than claims 26-30, there is no requirement that a patient maintain any visual acuity gain for a set duration—only that the patient "achieves the gain ***within***" the recited time period—here 52 weeks. Nor is there any requirement that every patient achieve the recited gain, only that such gains would be obvious for some patients receiving the dosing regimen—i.e. for "***a*** patient." *See,* Ex.1002, ¶166-167.

As an initial matter, as set out in Section VII, POSAs knew from the Phase I trial of aflibercept reported in the 2006 Press Release, that a single 2 mg dose in AMD patients produced a "mean improvement in BCVA [] 13.5 letters, with three of six patients gaining 15 or more letters" at six weeks. Ex.1027, 2. The described gain is "within" 52 weeks, and thus a POSA would have expected a visual acuity gain "within 52 weeks" for some patients from administration of the first dose in Dixon's dosing regimen alone. *See* Ex.1002, ¶168.

Additionally, the secondary endpoint of the VIEW 1 study for AMD, which used the dosing regimen described in Dixon, was the "proportion of patients who gained at least 15 letters of vision at week 52" as measured by ETDRS. Ex.1005, 1. A POSA would have found a visual acuity gain within the first 52 weeks for some patients receiving the Dixon dosing routine obvious and expected based on this knowledge. Ex.1002, ¶169. Additionally, Petitioner incorporates herein its discussion of claims 3-4 and 8-10 below, which address specific visual acuity gains and further demonstrates the obviousness of claim 1.

2. Claim 2

Dixon describes the visual acuity gains as BCVA according to ETDRS score throughout, and ETDRS is the "standard chart used in research to measure visual acuity." *See, e.g.,* Ex.1009, 1576; *see also* Ex.1002, ¶170; Ex.1006, 3. Thus, a

POSA would have found obvious to measure a gain in BCVA according to ETDRS letter score in the prior art clinical trials.

3. Claims 3-4 and 8-10

Claims 3-4 and 8-10 additionally require that "the patient gains at least [7, 8, or 9] letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" within 52 weeks or 24 weeks. Accordingly, if it was obvious to a POSA that a visual acuity gain of 9 letters would be achieved at least for some patients within 24 weeks, all of these claims are rendered obvious. *See* Ex.1002, ¶171-174.

As discussed above in claim 1, a POSA would have reasonably expected a gain of at least 15 letters—not just nine—for some patients within the first six weeks of treatment via the Dixon regimen (i.e. after at least the first dose). This is because the reported Phase I results for aflibercept showed 15 letter gains from a single 2mg/4mg injection. Ex.1002, ¶172; Ex.1027. This disclosures renders these additional claim limitations obvious. *Id.*

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

achieved a mean of 9 letter gains, ***with 29% gaining greater than 15 letters***, by 52 weeks. Ex.1009, 1576; *see also* Ex.1002, ¶173.

A POSA would have reasonably expected that at least some AMD patients, including those that achieved at least 15 letter gains, would have achieved a 9 letter visual acuity gain at some point during the first 24 weeks treatment via the Dixon dosing regimen based on knowledge of the effectiveness of a single dose and the further Phase II results. Ex.1002, ¶174. Dixon's loading/maintenance schedule would result in 8 overall doses during the year—two more doses than had been shown to produce 15 letter gains in over 1 in 4 patients. *Id*.

4. Claims 5 and 11

Claim 5 and 11 depend from claims 3 and 10 respectively and additionally recite that "only two secondary doses are administered to the patient." As discussed in Section VIII.D.3, Dixon renders obvious claims 3 and 10 and discloses the use of three monthly loading doses—an initial dose and "only two secondary doses." Ex.1009, 1576; *see also* Ex.1002, ¶175.

5. Claims 26-28

Claim 26 recites the same dosing regimen as claims 1 and 15, but further recites that the claimed method is "as effective in achieving a gain in visual acuity" as monthly administration of 0.5 of ranibizumab in AMD patients "at 52 weeks." Dependent claim 27 specifies only two secondary doses are given, as disclosed in

Dixon. *See* Section VII.D; Ex.1009. Dependent claim 28 recites the gain is measured using ETDRS, as also disclosed in Dixon. *Id.*; *see also* Ex.1002, ¶176.

As noted above, for purposes of this petition only, Petitioner assumes that to be "as effective" as monthly ranibizumab, a patient must achieve a gain of visual acuity between 8.1-9.4 letters, as reported in Table 1 of the '572 patent (Ex.1001, 13:5-35).

As discussed in connection with claims 1 and 3-4 and 8-10, Dixon renders obvious a substantially higher gain than 8.1-9.4 letters for some patients. Dixon reports that in the Phase II trial, AMD patients who received four initial monthly doses, followed by PRN dosing, received only an average of 1.6 additional injections beyond the initial doses through 52 weeks (for a total of ~5.6 doses in a year on average). Ex.1009, 1576. These patients achieved a mean of 9 letter gains, ***with 29% gaining greater than 15 letters, by 52 weeks***. *Id.*; *see also,* Ex.1002, ¶178.

A POSA would have found it obvious to apply the Dixon regimen to achieve the recited gains, and reasonably expected that when aflibercept, which produced superior gains and was known as the "most promising" anti-VEGF drug under investigation (Ex.1009, 1577), was administered according to the Dixon regimen, at least some AMD patients would have achieved the recited lower 7-9 letter gains using three initial monthly doses followed by 8-week maintenance dosing. Ex.1002, ¶¶179-181. This is because, as noted above, Dixon's dosing regimen (3 initial

monthly doses followed by 5 bi-monthly doses through week 52; 8 total) requires two additional doses than the Phase II PRN dosing regimen (4 initial monthly doses followed by 1.6 PRN doses; 5.6 total), which had already shown to achieve 15 letter gains for some patients. Ex.1009, 1576; Ex.1002, ¶¶179-181. In view of the Phase II PRN efficacy results, a POSA would have expected the additional doses of the Dixon regimen to produce similar gains and certainly substantially higher gains than just 8.1-9.4 letters. Ex.1002, ¶¶179-181.

Alternatively, 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 a modification was routine for a POSA. *See, e.g.*, Ex.1017, 23-24. Modifying the dosing regimen to provide four initial doses, for instance, would bring Dixon further closer to the Phase II regimen, but would provide five additional doses during the remaining 52 week period, rather than only the 1.6 mean doses given in the Phase II trial. *See* Ex.1002, ¶182. This would only serve to increase a POSA's reasonable expectation of producing a gain as effective as monthly ranibizumab. *Id.*

6. Claims 29-30

Claim 29 recites the same dosing regimen as claims 1, 15, and 26 but further recites that the claimed method is "as effective in maintaining visual acuity" as monthly administration of 0.5 of ranibizumab in AMD patients "at 52 weeks."

Dependent claim 30 further specifies that such maintenance "means loss of less than 15 letters" BCVA as measured by ETDRS. Accordingly, a POSA would need only to find it obvious that Dixon's dosing regimen merely prevented loss of more than 15 letters BCVA in some patients in order to be "as effective in maintaining visual acuity" as monthly ranibizumab at 52 weeks. As set out immediately above, a POSA would have found it obvious to apply Dixon's dosing regimen to produce visual acuity gains, not just maintenance above a loss of 15 letters. And because VEGF Trap-Eye/aflibercept has "higher binding affinity" to VEGF and likely "longer duration of effect in the eye" than ranibizumab, a POSA would have expected the maintenance of vision to be comparable to monthly ranibizumab. Ex.1009, 1577. Thus, for the same reasons recited above, these claims are obvious. *See*, Ex.1002, ¶183.

E. Ground V: Claims 16-17, and 20-21 Are Rendered Obvious by the 2009 Press Release Alone or in View of the 2007 ARVO Abstract, Dixon and/or the 2010 ARVO Abstract (collectively "Ground V References")

As set out above in Section VIII.A, the 2009 Press Release discloses every limitation of claim 15. The DME Results Claims depend from claim 15. Claim 16 recites a "gain in visual acuity within 52 weeks," while dependent claim 17 specifies the gain is at least 9 letters of BCVA in ETDRS. Dependent claim 21 recites the gain is lower—only 8 letters. Claim 20 depends from claim 17. Claim 17 recites a gain of 9 letters, and claim 20 further recites that the patient achieves the gain "within

24 weeks," not 52. Accordingly, the 2009 Press Release need only render obvious a gain of 9 letters within 24 weeks to render all of the DME Results Claims obvious. *See* Ex.1002, ¶¶184.

A POSA would have found it obvious to treat a patient via the disclosed regimen to achieve the recited 9 letter gain within 24 weeks, and would have expected that at least some patients, when treated via the 2009 Press Release dosing regimen, would achieve a 9 letter gain, which was modest compared to known gains for aflibercept and other anti-VEGF agents. Ex.1002, ¶¶185-190. As noted above, the Results Claims do not require the dosing regimen to apply to all patients populations in a one-size-fits-all approach. Instead, the claims are directed to a "method for treating diabetic macular edema in ***a*** patient." *See* Section V.C. Nor do they require that a patient maintain any visual acuity gain for a set duration—only that the patient "achieves the gain ***within***" the recited time period—here 24 or 52 weeks.

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

explains that the "primary efficacy endpoint evaluation is mean ***improvement*** in visual acuity at ***six months***." *Id.*; *see also*, Ex.1002, ¶186.

A POSA would have found it obvious to use the regimen disclosed for the Phase II trial for treatment of DME, involving the same number of initial loading doses as the VIEW 1 study, and would have expected to produce similar improvement ***for at least some patients*** as was expected to be produced in the VIEW 1 study. In other words, there would be nothing unexpected about a patient losing no less than or gaining at least 15 letters of vision (even if others did not). Ex.1002, ¶187.

This is particularly so given that, as set out in Section VII and reported in the ARVO 2007 Abstract and Dixon, it was known from the Phase I trial of aflibercept that a single 4mg dose in DME patients produced a "9 letters [gain in EDTRS] at four weeks….," well before the 24 week time frame recited in claim 20. Ex.1009, 1575; Ex.1030 ("Four patients had improvements in BCVA, ranging from 6 to 10 letters at 4 weeks post-injection."); Ex.1002, ¶189. A POSA would have reasonably expected the same gain would be produced by an initial set of three 2mg loading doses instead of a single 4mg dose, particularly given the successful use of initial loading doses in the context of AMD trials. *See* Section VII; *see also* Ex.1002, ¶¶43-49, 188 (explaining similarity in mechanism of action and results for AMD, DME).

Finally, a POSA would have found their expectation confirmed by data reported in April 2010 at the ARVO Annual Meeting in the 2010 ARVO Abstract. *See,* Ex.1002, ¶190. It was reported there that POSAs knew that that "[a]t 6 months [i.e. 24 weeks], the mean change in BCVA for each VTE arm ranged from +8.5 to +11.4 letters" gains had been achieved in the DME clinical trials described in the 2009 Press Release. Ex.1010, 1. This would confirm that it was obvious to apply the disclosed regimen, as well as a POSA's reasonable expectation that the 2009 Press Release regimen would produce 9 letter gains by 24 weeks.

F. Ground VI: Claims 6-7 and 12-13 Are Rendered Obvious by Each of Dixon in View of Hecht, Dixon in View of the 2006 Press Release and Hecht, and the December 2010 Press Release in View of Hecht

Claims 6-7 and 12-13 depend from claims 3 and 10 respectively and recite that the aflibercept is formulated as "an isotonic solution" and with a "nonionic surfactant." As set out in Grounds II and IV, claims 3 and 10 are anticipated by the December 2010 Press Release and rendered obvious by Dixon alone or in view of the 2006 Press Release. A POSA would have found the use of an isotonic formulation and nonionic surfactant in the disclosed formulation in these primary references obvious. Ex.1002, ¶¶191-194.

For instance, Dixon teaches that aflibercept is "formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye." Ex.1009, 1575. Dixon's

disclosure is consistent with how a POSA would have understood the aflibercept formulation in each primary reference. Ex.1002, ¶192. In particular, a POSA would understand that a non-isotonic formulation would irritate a patient's eye, and would expect an isotonic formulation to be used. *Id.*

This is confirmed by Hecht, which teaches the principles of formulation for ophthalmic solutions and specifically notes that such solutions must be "formulated to be sterile, ***isotonic*** and buffered for stability and comfort." Ex.1016, 1569; *Id*, 1571 ("[I]sotonicity always is desirable and particularly is important in intraocular solutions."). A POSA would have been motivated to make the aflibercept solution disclosed in the primary references isotonic to avoid irritation and would have a reasonable expectation in doing so, particularly given aflibercept was already known to be administered intravitreally. Ex.1002, ¶193.

Similarly, Hecht teaches that non-ionic surfactants are the "least toxic to ophthalmic tissues," "[a]id in achieving solution clarity," and can serve as "cosolvents to increase solubility." Ex.1016, 1571. Such surfactants also stabilize proteins such as aflibercept. Ex.1002, ¶194 (citing Ex.1032, 159). A POSA would have found it obvious that the formulations disclosed in the primary references would include a nonionic surfactant, would have been motivated to formulate aflibercept to achieve the known benefits, and would have had a reasonable expectation of doing so given aflibercept was already known to be administered

intravitreally and had been formulated with a non-ionic surfactant for other uses. *Id*., (citing Ex.1033 (Fraser), 1115).

G. Ground VII: Claims 18-19 and 22-23 Are Rendered Obvious by Each of the December 2010 Press Release in View of Hecht, and the 2009 Press Release in View of the Ground V References and Hecht

Claims 18-19 and 22-23 depend from claims 17 and 21 respectively and recite the same "an isotonic solution" and "nonionic surfactant" limitations addressed above. As set out in Grounds II and V, claims 17 and 21 are anticipated by the December 2010 Press Release and rendered obvious by the 2009 Press Release alone or in view of the Ground V References. For the same reasons set out in Ground VI (which is incorporated herein), these references in combination with Hecht render claims 18-19 and 22-23 obvious. Ex.1002, ¶195.

H. Ground VIII: Claim 14 Is Rendered Obvious by Each of Dixon and the December 2010 Press Release Alone or In View of the CATT Study and/or PIER Study

As set out in Section VI.B, the exclusion criteria should not be given patentable weight. Accordingly, these claims are rendered obvious for the same reasons as set forth in Grounds II and IV. Even if the exclusion criteria are given patentable weight, claim 14 is obvious. While the primary references do not recite exclusion criteria, the criteria were well known in the art and are disclosed therein. *See,* Ex.1002, ¶¶62-69, 196-203.

Specifically, the CATT and PIER Studies (Exs. 1020-26) described above in Section VII.H, included exclusion criteria for clinical trials of the leading intravitreally injected anti-VEGF treatments at the time. The exclusion criteria disclosed in these studies are the same as those claimed by the '572 patent, as is shown in Table 1 above in Section VII.H. There is nothing special regarding these criteria, and applying them in combination with the methods as described in connection with Grounds II and IV-V above renders the claimed method obvious. Ex.1002, 196-203.

Finally, POSAs would have been motivated to adopt the exclusion criteria in order follow the standard of care, as well as to solve a problem that references such as the 2009 Press Release and Dixon outline directly. *See* Ex.1002, ¶¶200-203. Applying the criteria would only increase a POSA's expectation of success in treatment. Ex.1021, 247; Ex.1034, Lucentis Label, 1; *see* Ex.1002, ¶¶200-203.

I. Ground IX: Claim 25 is Rendered Obvious by the 2009 Press Release Alone or in View of Shams or Elman 2010

Claim 25 depends from independent claim 15 and specifies that "four secondary doses are administered to the patient," meaning the dosing regimen consists of five initial monthly doses, followed by 8-week maintenance dosing (no "results limitations" are recited). This amounts to the same dosing regimen recited in the DME claims challenged in Petitioner's '601 IPR (IPR2023-00739).

The 2009 Press Release explicitly describes administering 2 mg aflibercept to treat DME using a number of different dosing regimens, including one consisting of three monthly loading doses followed by maintenance doses at 8-week intervals. Ex.1005.

The 2009 Press Release alone or in combination with Shams or Elman 2010 renders obvious claim 25. Ex.1002, ¶¶204-237. There is no special benefit taught in the '572 patent to using five loading doses as opposed to two, three, four, six, or more loading doses. The '572 patent states that "[t]he methods of the invention may comprise administering to the patient ***any number*** of secondary and/or tertiary doses of a VEGF antagonist" including "e.g. 2, 3, 4, 5, 6, 7, 8, or more." Ex.1001, 4:22-32.

Five loading doses is simply the number that works for ***some*** patients, and, importantly, the claims do not require the dosing regimen to apply to all patient populations in a one-size-fits-all approach. Nor could they, as there is no data in the patent supporting such a conclusion. Thus, the claims are directed to a "method for treating diabetic macular edema in ***a patient*** in need thereof," not an entire patient population or a percentage thereof, because that is all the specification describes. *See* Section V.C.

As set out above, the 2009 Press Release describes using ***three*** monthly loading doses followed by 8-week maintenance doses, among other regimens.

Ex.1005, 1. While three might be appropriate for some patients, a POSA would have understood that other patients would benefit from additional loading doses, including five monthly loading doses, and been motivated to provide those additional doses. Indeed, one of the other regimens recited in the 2009 Press Release is PRN ("as needed") dosing after three monthly doses, which requires routine monitoring and reinjection when needed. Ex.1005, 1.

Using five monthly loading doses is thus a trivial and routine modification that amounts to the addition of a single monthly injection between the last loading dose and first maintenance dose described in the 2009 Press Release. *See* Ex.1002, ¶¶204-212. A POSA would have found this sort of routine dose optimization obvious for patients still obtaining gains for monthly dosing, and it was also taught in the prior art. *Id.*; *see generally*, Ex.1002 ¶¶58-61.

In fact, the Shams reference explains that "[t]he specific time schedule [for administering doses of an anti-VEGF agent] can be readily determined by a physician having ordinary skill in administering the therapeutic compound ***by routine adjustments***…." Ex.1017, 23-24 (emphasis added). It further explains that "the time of administration of the number of first individual and second individual doses as well as subsequent dosages is adjusted to minimize adverse effects while maintaining a maximum therapeutic effect." *Id*. The 2009 Press Release alone or

in view of Shams thus renders the routine modification to five doses obvious. *See* Ex.1002, ¶¶204-216.

Similarly, the 2009 Press Release in combination with the teachings of Elman 2010 render the claims obvious. Ex.1002, ¶¶217-237. In the Elman 2010 trial, one of the subject groups was given four initial monthly loading doses, after which a clinician evaluated the subjects to determine if a fifth monthly dose of ranibizumab should be given. Ex.1018, Elman 2010. Elman 2010 reports that ***at least 78% of patients received a fifth loading monthly dose***. *Id.*, 4 (reporting that only 22% of patients did not receive a fifth dose). In view of Elman 2010, a POSA reviewing the 2009 Press Release's description of using three monthly loading doses would have been motivated to use the five loading doses that were shown by Elman to be efficacious in the vast majority of patients. *See* Ex.1002, ¶¶222-230

Notably, as set out above, to show the obviousness of the claims here, there is no requirement that a POSA would have been motivated to adopt five initial loading doses for ***all*** patients. But even if it were, 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 make five initial loading doses an obvious starting point for the treatment of all patients, even if in routine practice a POSA would in fact adjust the regimen from there. Ex.1018.

Finally, POSAs would have had a reasonable expectation of success in making and using the claimed combination, resulting in five initial loading doses instead of the three described in the 2009 Press Release.[9] Ex.1002, ¶¶231-237. The 2009 Press Release's disclosure of a Phase II trial using loading and maintenance dosing of aflibercept to treat DME would provide a POSA with a reasonable expectation of success that such a regimen would work, including the use of maintenance dosing. The claimed combination merely ***adds*** one additional dose to the DME regimen with 3 monthly loading doses followed by 8-week maintenance doses disclosed in the 2009 Press Release. Ex.1002, ¶¶210, 231-237. 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. *Id.*; Ex.1009; Ex.1005.

J. Grounds X and XI

1. The "Results Limitations" in the Results Claims Are Not Entitled to Patentable Weight

The independent claims of the Results Claims contain "results limitations" which recite "wherein the patient achieves…", "wherein the patient gains…", or

[9] There is no requirement of certainty; "[f]or obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

"wherein the method is as effective…." Because they appear in "wherein" clauses and are not recited as an affirmative step, to be positive limitations entitled to patentable weight, the "results limitations" must provide structure or acts necessary to define the invention. *In re Kubin*, 561 F.3d 1351, 1353 (Fed. Cir. 2009). But while these clauses might ***imply*** some affirmative act, such as measuring the patient's visual acuity, they do not ***require*** one. The "results limitations" plainly state ***only*** a result—i.e. "wherein the patient ***achieves***…", etc. They are thus not entitled to patentable weight.

Specifically, these limitations in the Results Claims do not change or alter ***any*** steps of the method, and thus are not entitled to patentable weight. Instead, the claim defines the affirmative steps of the method by specifying the dosing regimen, and the "wherein" clauses are merely an intended result, nothing more. *Id.* The Patent Owner chose to claim the "results limitations" in this manner; it should not now be allowed to rewrite the "wherein" clauses as anything other than intended results.

Indeed, the district court in the Mylan Litigation applied the same reasoning in finding that the "Best Corrected Visual Acuity" limitations of the Challenged Claims lacks patentable weight. Ex.1063, 37-39 (finding that the BCVA limitation is informational, does not change the manipulative steps of the claims, and has no patentable weight.). Specifically, the court noted "[t]here is no change or modification to the underlying dosing regimen if the [BCVA gain] test result is

obtained, or not" and "[a]n old method of treating patients cannot be made new by describing the results that a patient can get from the treatment method whether those results involve…achieving certain test results." *Id.*

The same conclusion is warranted here. Intended results should not be given patentable weight. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (holding that "in a stabilizing amount" as recited in the body of a claim was non-limiting because it "simply describes the intended result of using the weight to volume rations in the claims); *Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp.*, 86 F. Supp. 2d 433, 443 (D.N.J.) *aff'd in relevant part*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) (holding "reduced hematologic toxicity" not limiting as a matter of claim construction because it did not "result in a manipulative difference in the steps of the claim."); *In Re: Copaxone Consol. Cases*, 906 F.3d 1013 (Fed. Cir. 2018).

Petitioner notes that while the Board relied on *Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center v. Eli Lilly & Co.*, 849 F.3d 1049 (Fed. Cir. 2017) ("*UCLA*.") in ruling on Apotex's '572 Petition, the claims here are meaningfully different from those in *UCLA* in ways not identified by Apotex.

In *UCLA.*, the Federal Circuit accorded patentable weight to a claim with two steps, the second of which recited "b) arresting or regressing the at least one of the

penile tunical fibrosis and corporal tissue fibrosis, wherein the PDE-5 inhibitor is administered at a dosage up to 1.5 mg/kg/day for not less than 45 days." *Id*., 1060-61. The Federal Circuit held that the "arresting or regressing language" should be given patentable weight for at least two reasons, neither of which apply here.

First, the Federal Circuit reasoned that "[w]hile not dispositive, it is significant that the phrase 'arresting or regressing the [penile] fibrosis' is drafted as part of a separate step of the method…." *Id*., 1061. The Federal Circuit held this distinguished the structure of the claims at issue from past cases where the relevant language appeared in the "structure of patent claims in which statements of general purpose" were made, such as the preamble, and were held to be non-limiting. *Id*.

Second, the Federal Circuit also noted that "[b]ecause the '903 patent claims specify only a maximum dosage level and a minimum treatment period, it is different from cases in which the claims contain express dosage amounts as material claim limitations." *Id*.

Neither of the reasons the Federal Circuit gave for finding the language limiting apply here.

First, as noted above, the relevant language is not recited as "part of a separate step of the method," but rather as part of "wherein" clauses—i.e. "[w]herein the patient achieves…" a result. "A whereby [or wherein] clause in a method claim is not given weight when it simply expresses the intended result of a process step

positively recited" or that is otherwise inherent. *Minton v. Nat'l Ass'n. of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381, (Fed. Cir. 2003); *see also Lockheed Martin Corp. v. Space Systems/Loral, Inc.*, 324 F.3d 1308, 1319 (Fed. Cir. 2003) (language only stated an inherent result); *Kubin*, 561 F.3d, 1357 (irrelevant whether prior art disclosed a feature "wherein the polypeptide binds CD48" when feature was necessarily present in protein).

"Wherein" clause language must provide structure or acts necessary to define the invention to be a positive limitation. *Kubin*, 561 F.3d, 1353. Here, as set out above, the "results limitations" language does not define the invention—it provides no "structure or acts" at all, just results of practicing the claimed method.

Second, and unlike the claims in *UCLA*. which specified "only a maximum dosage level and a minimum treatment period," the claims here "contain express dosage amounts [2mg] as material claim limitations, and in which efficacy is 'inherent in carrying out the claim steps.'" *Id.*, 1061. There is thus no need to give patentable weight to the language to put a limit on the scope of the claim, as was done in *UCLA*.

Accordingly, Petitioner respectfully submits that the "results limitations" in the Results Claims lack patentable weight.

2. Ground X: Claims 1-5, 8-11, and 26-30 are Anticipated by Dixon Because the "Results Limitations" Lack Patentable Weight

As set out in Ground IV, Dixon expressly discloses all of the limitations of the Generic/AMD Results Claims other than the "results limitations." These limitations are not entitled to patentable weight as set out in Section VIII.J.1 above, and thus Dixon anticipates these claims for the reasons set out in Ground IV. *See* Ex.1002, ¶238.

3. Ground XI: Claims 1-5, 8-11, 16-17, and 20-21 are Anticipated by the 2009 Press Release Because the "Results Limitations" Lack Patentable Weight

As set out in Ground V, the 2009 Press Release expressly discloses all of the limitations of the Generic/DME Results Claims other than the "results limitations." As set out immediately above, these limitations are not entitled to patentable weight, and thus the 2009 Press Release anticipates these claims for the reasons set out in Ground V. Ex.1002, ¶239.

K. There Are No Secondary Considerations

Finally, though it is not Petitioner's burden, Patent Owner cannot establish secondary considerations that would support a finding of non-obviousness, and particularly it cannot overcome the strong *prima facie* case of obviousness presented in Grounds IV-IX. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); Ex.1002, ¶¶240-245.

No Unexpected Results. Patent Owner's anticipated argument—asserted during prosecution of related claims in the family (Ex.1055, '681 patent PH, 488-

493)—that the less frequent regimen of the Challenged Claims produced "unexpected results" is incorrect. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006); *In re Kao*, 639 F.3d 1057, 1068-69 (Fed. Cir. 2011); Ex.1002, ¶242. As set out in Sections VIII.D-E and VIII.I, the Results Claims recite obvious results based on the disclosure of the claimed method.

No Long-Felt, Unmet Need. Patent Owner cannot establish a "need" or show that any such need was "long-felt." Any purported need for the claimed dosing regimens had been fulfilled long before the '572 patent was filed. Ex.1002, ¶243. Indeed, POSAs had been implementing such regimens for DME and AMD well before the priority date. *Id*. And other successful, intravitreally injected anti-VEGF treatments existed. *Id.*

No Nexus. Patent Owner cannot establish nexus to the "merits of the claimed invention" of the '572 patent because the art discloses all of the claimed elements. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330–31 (Fed. Cir. 2017) (citing *Kao*, 639 F.3d at 1068). There is no "novel combination or arrangement of known individual elements" in the recited limitations—rather, they are routine. Ex.1002, ¶244.

IX. DISCRETIONARY DENIAL IS UNWARRANTED

Discretionary denial is unwarranted here.

A. The *Becton Dickinson* Factors Do Not Favor Denial Under 35 U.S.C. § 325(d)

The Board uses a two-part framework to analyze whether denial under § 325(d) is proper. The Board considers several nonexclusive factors ("*Becton Dickinson* factors") within this framework to provide useful insight into how to apply each prong, each of which is discussed below. *Id.*, 4; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph).

1. *Becton Dickinson* Factors (a), (b), and (d)

Petitioner's arguments and prior art here are neither the same nor substantially the same art or arguments previously before the Office during prosecution of the '572 patent.

First, as set out in Section V.D, the Examiner only issued non-statutory double patenting rejections during prosecution and no § 102 or § 103 rejections. Petitioner asserts anticipatory references and combinations involving references never expressly considered during prosecution that provide additional, non-cumulative disclosures, including the 2009 and 2010 Press Releases and Dixon. In other words, the art and arguments presented here were neither "involved" nor "evaluated" during prosecution, and therefore, they are not the same or substantially the same as that

previously considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. § 325(d).

Patent Owner may argue that the Press Releases and Dixon were identified on the Information Disclosure Statements along with hundreds of other references and marked "considered" by the Examiner during prosecution. But, the Examiner did not consider any combination of the art and arguments presented here, including the 2009 Press Release, December 2010 Press Release, and November 2010 Press Release, opting instead to issue non-statutory obviousness-type double patenting rejections over prior Regeneron patents. *See* Section V.C. "The Board has consistently declined exercising its discretion under Section 325(d) when[, as here] the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, 62 (Aug. 30, 2019).

2. *Becton Dickinson* Factors (c), (e), and (f)

Because Petitioner presents new arguments and combinations herein, analysis of *Becton Dickinson* factors (c), (e), and (f) is unnecessary. Even if the grounds presented herein were considered previously presented to the Office somehow, however, the Examiner made clear errors in evaluating the art.

In particular, as discussed in Section V.D, the Examiner issued obviousness-type double patenting rejections but after a terminal disclaimer, failed to make an

obviousness rejection over, for instance, the 2009 Press Release that also disclosed the identical dosing regimen to the reference patents. Applicants thus were allowed the claims without ever addressing the substance of the Examiner's obviousness rejection. This was clear error.

As set out in Sections VIII, the claims should be found both anticipated and obvious over the dosing regimens in the 2009 Press Release, 2010 Press Releases, and Dixon. The Examiner failed to apply the same (correct) logic applied in evaluating the reference patents to an evaluation of the prior art, constituting material error.

B. The *General Plastic* Factors Do Not Support Denial Under 35 U.S.C. § 314(a)

General Plastic is applicable to a petition that challenges the same patent as a previous petition. IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017) (precedential), slip op. 9-10. It favors institution here.

The primary *General Plastic* factor examines "whether the ***same*** petitioner previously filed a petition directed to the ***same claims***…." *Qualcomm Inc. v. Monterey Research, LLC*, IPR2020-01493, Paper 11, 15 (March 8, 2021). The purpose of this inquiry is primarily to determine whether the petition seeks to harass or burden the Patent Owner, or to gain strategic advantage through serial filings. But in this case, Petitioner had nothing to do with Apotex's petition, and Petitioner

challenges a new set of claims—the DME claims—in addition to those challenged in Apotex's petition by asserting a new set of arguments.

In addition to these fundamental differences, there is no other evidence that Petitioner seeks to harass or unduly burden Patent Owner with its petition. Quite the opposite: while Apotex previously filed a petition, the instant petition challenges DME claims that Apotex did not challenge and presents entirely new grounds of unpatentability, including obviousness arguments as to the Results Claims that Apotex inexplicably failed to make. Petitioner is merely trying to set out an adequate challenge where Apotex failed. Petitioner should not be denied the opportunity to challenge the full set of '572 claims by Apotex's prior, failed arguments—Petitioner had nothing to do with them.

A prior failed petition is not a bar to subsequent institution, as shown by, for instance *Sanofi-Aventis U.S. LLC v. Immunex Corp*., IPR2017-01884, Paper No. 14 (PTAB Feb. 15, 2018). There, the same Petitioners filed three separate requests for an *inter partes review* (IPR) of the same claims. Their third request was instituted after the first two were denied. *Id*. And the facts here are substantially more favorable to Petitioner than in *Sanofi*, given Petitioner had nothing to do with the first Apotex Petition.

It thus would be unfair to discretionarily deny Petitioner's petition merely because a prior, independent challenger filed earlier against a limited set of claims,

asserting an unduly limited set of art and arguments, and failed. And it would make no sense to penalize Petitioner for filing after the Board's decision to deny institution, as Grounds I-IX of the petitioner present new art and arguments that have nothing to do with Apotex's reliance on patentable weight and inherency arguments, and thus cannot support a claim of "roadmapping."

The fact that there is no evidence Petitioner is seeking to burden Patent Owner with serial petitions should "weigh[] especially heavily against a discretionary denial." *See Unified Patents, Inc. v. Certified Measurement, LLC*, IPR2018-00548, Paper 7, 7-8 (Sept. 5, 2018).

Absent "extenuating circumstances" such as a showing of coordination between petitioners, once resolution of factor 1 indicates that Petitioner had not previously filed a petition against the same patent claims, factors 2-5 bear little relevance. *Qualcomm*, Paper 11, 15 (March 8, 2021). As set out above, there are no such extenuating circumstances here. There was no coordination between Apotex and Petitioner or any other relationship as to the preparation of this petition.

C. The *Fintiv* Factors Do Not Support Denial Under 35 U.S.C. § 314(a)

The *Fintiv* factors do not favor a discretionary denial. Petitioner is not involved in any parallel litigation with Patent Owner and has no control over what claims or patents are asserted in the Mylan Litigation, making *Fintiv* inapplicable.

Moreover, at least claim 15—the DME claim—is not being litigated in the Mylan Litigation (Ex.1062, Mylan April 10 Motion), and it is highly likely that none of the DR/DME claims are being asserted, given that Mylan chose ***not*** to challenge the DR/DME claims in its '601 IPR.

Beyond the certainty that claim 15 will not be litigated, Petitioner challenges 30 claims here, whereas Regeneron must narrow its asserted claims to 12 claims from three patents. *Id*. It is thus a certainty that at least 20 of the claims challenged here will ***not*** be addressed in the Mylan Litigation. Regardless, Patent Owner should not be allowed to argue Petitioner's petition should be dismissed on discretionary grounds without committing to litigate the Challenged Claims in that litigation.

X. CONCLUSION

For the foregoing reasons, Petitioner has established a reasonable likelihood that claims 1-30 are unpatentable. Petitioner therefore respectfully requests that *inter partes* review of the '572 patent be granted.

DATED: April 27, 2023

Respectfully submitted,

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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(a)(1)(i) and (b)(1)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, it contains 13,996 words as counted by the word processing program used to prepare the paper.

Date: April 27, 2023

Respectfully submitted,

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CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that true and correct copies of Petitioner's Power of Attorney, Petition for *Inter Partes* Review of U.S. Patent No. 11,253,572, and Exhibits 1001-1064 were served on April 27, 2023 via FedEx Priority Overnight on Patent Owner at the correspondence address of record for U.S. Patent No. 11,253,572 as evidenced in in Patent Centers:

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