UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,

Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,

Patent Owner

Inter Partes Review No.: IPR2022-00301

U.S. Patent No. 9,669,069 B2
Filed: December 17, 2015
Issued: June 6, 2017
Inventor: George D. Yancopoulos

Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,669,069 B2

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Other Authorities

Regulations

EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 9,669,069 B2 ("'069 patent")
1002	Expert Declaration of Dr. Thomas A. Albini in Support of Petition for *Inter Partes* Review of Patent No. 9,669,069 B2, dated May 4, 2021 ("Albini")
1003	Expert Declaration of Mary Gerritsen, Ph.D. in Support of Petition for *Inter Partes* Review of U.S. Patent No. 9,669,069 B2, dated Apr. 26, 2021("Gerritsen")
1004	Jocelyn Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 PROC. NAT'L ACAD. SCI. 11393 (2002) ("Holash")
1005	Quan Dong Nguyen et al., *A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration*, 116 OPHTHALMOLOGY 2141 (2009) ("Nguyen-2009")
1006	James A Dixon et al., *VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration*, 18 EXPERT OPINION ON INVESTIGATIONAL DRUGS 1573 (2009) ("Dixon")
1007	Adis R&D Profile, *Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye*, 9 DRUGS R&D 261 (2008) ("Adis")
1008	U.S. Patent No. 7,531,173 B2 ("'173 patent")
1009	U.S. Patent No. 7,396,664 B2 ("'664 patent")
1010	U.S. Patent No. 7,374,758 B2 ("'758 patent")
1011	F Semeraro et al., *Aflibercept in Wet AMD: Specific Role and Optimal Use*, 7 DRUG DESIGN, DEV. & THERAPY 711 (2013) ("Semeraro")

1012	Press Release, Regeneron, Regeneron and Bayer Health Care Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration (Apr. 28, 2008), http://investor.regeneron.com/releasedetail.cfm?releaseid=394066 ("Regeneron (28-April-2008)")
1013	Press Release, Regeneron, Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration (May 8, 2008),http://investor.regeneron.com/releasedetail.cfm?ReleaseID=394065 ("Regeneron (8-May-2008)")
1014	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1), NCT00509795, ClinicalTrials.gov (Apr. 28, 2009), https://clinicaltrials.gov/ct2/show/NCT00509795 ("NCT-795")
1015	VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2), NCT00637377, ClinicalTrials.gov (Mar. 17, 2008), https://clinicaltrials.gov/ct2/show/NCT00637377 ("NCT-377")
1016	U.S. Patent Nos. 7,303,746 B2; 7,303,747 B2; 7,306,799 B2; and 7,521,049 B2 ("Monthly-Dosing-Patents")
1017	File History of U.S. Patent No. 9,669,069 B2 ("'069 FH")
1018	Jeffrey S. Heier et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration*, 119 OPHTHALMOLOGY 2537 (2012) ("Heier-2012")
1019	U.S. Patent No. 9,254,338 B2 ("'338 patent")
1020	Jeffrey S. Heier, *Intravitreal VEGF Trap for AMD: An Update*, RETINA TODAY, Oct. 2009, 44 ("Heier-2009")
1021	Regeneron Pharm., Inc., Quarterly Report (Form 10-Q) (Sept. 30, 2009) ("2009 10-Q")
1022	U.S. Patent No. 7,374,757 B2 ("'757 patent")

1023	U.S. Patent No. 7,070,959 B1 ("'959 patent")
1024	File History of U.S. Patent No. 7,374,758 B2, 12/22/2011 Patent Term Extension Application ("'758 FH, 12/22/2011 PTE")
1025	Michael Engelbert et al., *Long-Term Follow-Up For Type 1 (Subretinal Pigment Epithelium) Neovascularization Using A Modified "Treat And Extend" Dosing Regimen of Intravitreal Antivascular Endothelial Growth Factor Therapy*, 30 RETINA, J. RETINAL & VITREOUS DISEASES 1368 (2010) ("Engelbert-2010")
1026	Michael Engelbert et al., *"Treat and Extend" Dosing of Intravitreal Antivascular Endothelial Growth Factor Therapy For Type 3 Neovascularization/Retinal Angiomatous Proliferation*, 29 J. RETINAL & VITREOUS DISEASES 1424 (2009) ("Engelbert-2009")
1027	Richard F. Spaide et al., *Prospective Study of Intravitreal Ranibizumab as a Treatment for Decreased Visual Acuity Secondary to Central Retinal Vein Occlusion*, 147 AM. J. OPHTHALMOLOGY 298 (2009) ("Spaide")
1028	Press Release, Regeneron, Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion (Apr. 30, 2009), https://investor.regeneron.com/news-releases/news-release-details/bayer-and-regeneron-extend-development-program-vegf-trap-eye ("Regeneron (30-April-2009)")
1029	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO), NCT01012973, ClinicalTrials.gov (Nov. 12, 2009), https://clinicaltrials.gov/ct2/show/NCT01012973 ("NCT-973")
1030	P Mitchell et al., *Ranibizumab (Lucentis) in Neovascular Age-Related Macular Degeneration: Evidence from Clinical Trials*, 94 BRIT. J. OPHTHALMOLOGY 2 (2009) (date of online publication) ("Mitchell")
1031	Pascale G. Massin, *Anti-VEGF Therapy for Diabetic Macular Edema: An Update*, RETINA TODAY, SEPT./Oct. 2008, 54 ("Massin")

1032	Press Release, Bayer AG, Bayer and Regeneron Start Additional Phase 3 Study for VEGF Trap-Eye in Wet Age-Related MacularDegeneration (May 8, 2008) ("Bayer (8-May-2008)")
1033	U.S. Patent Application Publication No. 2006/0217311 A1 ("Dix")
1034	Anne E. Fung et al., *An Optical Coherence Tomography-Guided, Variable Dosing Regimen with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration*, 143 AM. J. OPHTHALMOLOGY 566 (2007) ("Fung")
1035	Geeta A. Lalwani et al., *A Variable-dosing Regimen with Intravitreal Ranibizumab for Neovascular Age-Related Macular Degeneration: Year 2 of the PrONTO Study*, 148 AM. J. OPHTHALMOLOGY 43 (2009) ("Lalwani")
1036	Peter A Campochiaro et al., *Ranibizumab for Macular Edema Due to Retinal Vein Occlusions: Implication of VEGF as a Critical Stimulator*, 16 MOLECULAR THERAPY 791 (2008) ("Campochiaro")
1037	Robert Steinbrook, *The Price of Sight — Ranibizumab, Bevacizumab, and the Treatment of Macular Degeneration*, 355 N. ENG. J. MED. 1409 (2006) ("Steinbrook")
1038	Curriculum Vitae of Dr. Thomas Albini ("Albini CV")
1039	U.S. Patent No. 7,378,095 B2 ("'095 patent")
1040	*International Nonproprietary Names for Pharmaceutical Substances (INN)*, 20 WHO DRUG INFORMATION 115 (2006) ("WHO Drug Info")
1041	Press Release, Regeneron, Regeneron Reports Full Year and Fourth Quarter 2008 Financial and Operating Results (Feb. 26, 2009), https://investor.regeneron.com/news-releases/news-release-details/regeneron-reports-full-year-and-fourth-quarter-2008-financial ("Regeneron (26-February-2009)")

1042	U.S. DEP'T HEALTH & HUMAN SERVS., NAT'L INST. HEALTH, NAT'L EYE INST., *Age-Related Macular Degeneration: What You Should Know* (Sept. 2015), https://www.nei.nih.gov/sites/default/files/health-pdfs/WYSK AMD English Sept2015 PRINT.pdf ("NIH AMD")
1043	David M. Brown & Carl D. Regillo, *Anti-VEGF Agents in the Treatment of Neovascular Age-Related Macular Degeneration: Applying Clinical Trial Results to the Treatment of Everyday Patients*, 144 AM. J. OPHTHALMOLOGY 627 (2007) ("Brown")
1044	U.S. DEP'T HEALTH & HUMAN SERVS., NAT'L INST. HEALTH, NAT'L EYE INST., *Diabetic Retinopathy: What You Should Know* (Sept. 2015), https://www.nei.nih.gov/sites/default/files/2019-06/Diabetic-Retinopathy-What-You-Should-Know-508.pdf ("NIH DR")
1045	Napoleone Ferrara & Kari Alitalo, *Clinical Applications of Angiogenic Growth Factors and Their Inhibitors*, 5 NATURE MED. 1359 (1999) ("Ferrara-1999")
1046	Napoleone Ferrara & Robert S. Kerbel, *Angiogenesis as a Therapeutic Target*, 438 NATURE 967 (2005) ("Ferrara-2005")
1047	Ziad F. Bashshur et al., *Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration*, 142 AM. J. OPHTHALMOLOGY 1 (2006) ("Bashshur")
1048	LUCENTIS® Prescribing Information (2006) ("Lucentis")
1049	L. Spielberg & A. Leys, *Intravitreal Bevacizumab for Myopic Choroidal Neovascularization: Short-Term and 1-Year Results*, 312 BULLETIN SOCIETE BELGE D'OPHTALMOLOGIE 17 (2009) ("Spielberg")
1050	Ursula Schmidt-Erfurth, *Current Concepts in the Management of Diabetic Macular Edema*, 7 PROCEEDINGS 52 (2010) ("Schmidt-Erfurth")
1051	Pearse A. Keane et al., *Effect of Ranibizumab Retreatment Frequency on Neurosensory Retinal Volume in Neovascular AMD*,

	29 RETINA 592 (2009) ("Keane")
1052	J.S. Rudge 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*, 70 COLD SPRING HARBOR SYMPOSIA QUANTITATIVE BIOLOGY 411 (2005) ("Rudge")
1053	Press Release, Regeneron, Positive Interim Phase 2 Data Reported for VEGF Trap-Eye in Age-Related Macular Degeneration (Mar. 27, 2007), https://newsroom.regeneron.com/news-releases/news-release-details/positive-interim-phase-2-data-reported-vegf-trap-eye-age-related?releaseid=394105 ("Regeneron (27-March-2007)")
1054	Press Release, Regeneron, Regeneron and Bayer Healthcare Initiate Phase 3 Global Development Program for VEGF Trap-Eye in Wet Age-Related Macular Degeneration (AMD) (Aug. 2, 2007), https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-bayer-healthcare-initiate-phase-3-global ("Regeneron (2-August-2007)")
1055	Retina Society, VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results, A Phase 2, Randomized, Controlled Dose-and Interval-Ranging Study of Intravitreal VEGF Trap-Eye in Patients With Neovascular, Age-Related Macular Degeneration (Sept. 28, 2008) ("Retina Society Meeting Presentation")
1056	Press Release, Regeneron, VEGF Trap-Eye Final Phase 2 Results in Age-related Macular Degeneration Presented at 2008 Retina Society Meeting (Sept. 28, 2008), https://investor.regeneron.com/news-releases/news-release-details/vegf-trap-eye-final-phase-2-results-age-related-macular?ReleaseID=393906 ("Regeneron (28-September-2008)")
1057	Press Release, Regeneron, VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients with Diabetic Macular Edema (Feb. 18, 2010), https://investor.regeneron.com/news-releases/news-release-details/vegf-trap-eye-shows-positive-results-phase-2-study-patients?releaseid=445521 ("Regeneron (18-February-2010)")

1058	ASS'N FOR RES. VISION & OPHTHALMOLOGY, ARVO® News (Winter/Spring 2008) ("ARVONews Winter/Spring 2008")
1059	ASS'N FOR RES. VISION & OPHTHALMOLOGY, ARVO® News (Summer 2007) ("ARVONews Summer 2007")
1060	Jean-François Korobelnik et al., *Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion*, 121 OPHTHALMOLOGY 202 (2014) ("Korobelnik")
1061	Curriculum Vitae of Dr. Mary Gerritsen ("Gerritsen CV")
1062	EP 2 663 325 (published as WO 2012/097019 (A1)) ("EP-325")
1063	File History of EP 2 663 325 ("EP-325-FH")
1064	BMJ Publishing Group Ltd., *Online First*, BJO ONLINE, (Feb. 11, 2009), https://bjo.bmj.com/onlinefirst.dtl [http://web.archive.org/web/20090212162702/https://bjo.bmj.com/onlinefirst.dtl] ("Wayback-BJO-Online First")
1065	BMJ Publishing Group Ltd., *Review: Ranibizumab (Lucentis) In Neovascular Age-Related Macular Degeneration: Evidence From Clinical Trials*, BRITISH J. OPHTHALMOLOGY (Dec. 2020), https://bjo.bmj.com/content/94/1/2.altmetrics ("BJO-Article Metrics")
1066	Press Release, Bayer, VEGF Trap-Eye Shows Positive Results in Phase II Study in Patients with Diabetic Macular Edema (Feb. 18, 2010) ("Bayer (18-February-2010)")
1067	Press Release, Bayer, Bayer HealthCare and Regeneron Announce Encouraging 32-Week Follow Up Results From A Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration (Apr. 28, 2008) ("Bayer (28-April-2008)")
1068	Press Release, Regeneron, Enrollment Completed in Regeneron and Bayer Healthcare Phase 3 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD) (Sept. 14, 2009), https://newsroom.regeneron.com/news-releases/news-release-details/enrollment-completed-regeneron-and-bayer- healthcare-phase-3

	("Regeneron (14-September-2009)")
1069	ClinicalTrials.gov, *What Is ClinicalTrials.gov?*, U.S. NAT'L LIBRARY MED. (Jan. 2018), https://www.clinicaltrials.gov/ct2/about-site/background ("Background-ClinicalTrials.gov")
1070	Affidavit of Duncan Hall (Internet Archive Records Request Processor) Regarding Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO), NCT01012973, ClinicalTrials.gov (Apr. 8, 2011); Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1), NCT00509795, ClinicalTrials.gov (Apr. 8, 2011); and VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2), NCT00637377, ClinicalTrials.gov (Aug. 13, 2009), dated January 20, 2021 ("Wayback-Affidavit-069")
1071	Frank G Holz et al., *VEGF Trap-Eye for Macular Oedema Secondary to Central Retinal Vein Occlusion: 6-Month Results of the Phase III GALILEO Study*, 97 BRITISH J. OPHTHALMOLOGY 278 (2013) ("Holz")
1072	Janice M. Reichert, *Antibody-Based Therapeutics To Watch In 2011*, 3 MABS 76 (2011) ("Reichert")
1073	Owen A. Anderson et al., *Delivery of Anti-Angiogenic Molecular Therapies for Retinal Disease*, 15 DRUG DISCOVERY TODAY 272 (2010) ("Anderson")
1074	Thomas A. Ciulla & Philip J. Rosenfeld, *Antivascular Endothelial Growth Factor Therapy For Neovascular Age-Related Macular Degeneration*, 20 CURRENT OPINION OPHTHALMOLOGY 158 (2009) ("Ciulla")
1075	Zhang Ni & Peng Hui, *Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration*, 223 OPHTHALMOLOGICA 401 (2009) ("Ni")

1076	Marco A. Zarbin & Philip J. Rosenfeld, *Pathway-Based Therapies for Age-Related Macular Degeneration: An Integrated Survey of Emerging Treatment Alternatives*, 30 RETINA 1350 (2010) ("Zarbin")
1077	Corporate Finance Institute, *SEC Filings: Public Disclosures About Public Companies*, https://corporatefinanceinstitute.com/resources/data/public-filings/sec-filings/ (last visited May 5, 2021) ("Corporate Finance Institute")
1078	Carl W. Schneider, *Nits, Grits, and Soft Information in SEC Filings*, 121 U. PA. L.REV. 254 (1972) ("Schneider")
1079	Justin Kuepper, *The Best Investment Information Sources: Using SEC Filings, Analyst Reports, and Company Websites*, BALANCE (Jan. 13, 2021), https://www.thebalance.com/top-best-sources-of-investor-information-1979207 ("Kuepper")
1080	Kristina Zucchi, *EDGAR: Investors' One-Stop-Shop For Company Filings*, YAHOO!LIFE (Jan. 31, 2014), https://www.yahoo.com/lifestyle/tagged/health/edgar-investors-one-stop-shop-170000800.html ("Zucchi")
1081	Adam Hayes, *SEC Filings: Forms You Need To Know*, INVESTOPEDIA (Jan. 18, 2021), https://www.investopedia.com/articles/fundamental-analysis/08/sec-forms.asp ("Hayes")
1082	Amino acid sequence alignment of SEQ ID NO:2 of the '069 patent with SEQ ID NO:16 of the '758 patent and SEQ ID NO:4 of Dix ("'069 Amino Acid Sequences")
1083	Nucleotide sequence alignment of SEQ ID NO:1 of the '069 patent with SEQ ID NO:15 of the '758 patent and SEQ ID NO:3 of Dix ("'069 Nucleotide Sequences")

I. INTRODUCTION.

Apotex Inc. ("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 and 8-12 (the "Challenged Claims") of U.S. Patent No. 9,669,069 ("'069 patent") (Ex.1001), assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

II. OVERVIEW.

The Challenged Claims are drawn to nothing more than a known, mental step dosing regimen (i.e., "as-needed" or "*pro re nata*" ("PRN") administration) using a drug known to persons of ordinary skill in the art (referred to herein as a "skilled artisan(s)") to treat angiogenic eye disorders. These claims should have never issued. Each is anticipated and obvious over the prior art, which expressly disclosed skilled artisans actively practicing these exact methods on patients—with success. Indeed, Regeneron's own clinical trials for EYLEA® (aka "VEGF Trap-Eye" or "aflibercept")—widely published—utilized the claimed PRN dosing regimen to treat age-related macular degeneration ("AMD") years before Regeneron filed the '069 patent application in 2011. Regeneron withheld those publications from the Examiner, allowing the '069 patent to issue.

By 2010, ophthalmologists were moving away from monthly dosing regimens for vitreoretinal disease therapies due to problems with patient compliance and

discomfort associated with intravitreal injections. For example, in 2007, LUCENTIS® (ranibizumab), an anti-VEGF therapy approved for monthly dosing,[1] was undergoing a series of clinical trials to assess less frequent dosing regimens. These clinical assessments included, *inter alia*, PRN dosing (including, PRN after three monthly loading doses). Motivated to keep pace with the LUCENTIS® trials, Regeneron initiated a clinical program for EYLEA® that implemented those same regimens—e.g., Regeneron's Phase 2 clinical trials for age-related macular degeneration ("CLEAR-IT-2") assessing PRN dosing after four monthly doses. The problem: this trial regimen was widely launched, published and thus known to skilled artisans long before 2011. The prior art includes numerous Regeneron press releases, which were directed to skilled artisans to attract their interest in EYLEA®, along with publications directed to practicing ophthalmologists. Many disclosed the CLEAR-IT-2 trial details, including, most notably, the later-claimed PRN dosing regimen. Those public disclosures render the Challenged Claims unpatentable.

Petitioner files this Petition and supporting expert declarations from: (i) renowned ophthalmologist, Dr. Thomas Albini (Ex.1002), to apprise the Board of invalidating prior art—much of which was not before the Examiner when prosecuting the '069 patent; and (ii) Dr. Mary Gerritsen, a pharmacologist with over

[1] LUCENTIS® is the primary competitor to EYLEA®.

thirty years' experience, (Ex.1003) to confirm the public availability of certain prior art disclosures relied upon herein.

Anticipation. Challenged Claims 1 and 9-12 are anticipated by three separate prior art references: Dixon, Heier-2009, and Regeneron (30-April-2009). Dixon and Heier-2009 disclose Regeneron's Phase 2 CLEAR-IT-2 trial. Regeneron (30- April-2009) discloses Regeneron's Phase 3 RVO trial regimen.

Further, claims 1 and 8-12 are anticipated by Dixon in light of arguments that Regeneron itself made during prosecution of the '069 patent. Dixon discloses Regeneron's Phase 3 AMD (VIEW1/VIEW2) trial, which evaluated every-eight-week dosing (following a fixed monthly loading dose period)—a regimen Regeneron told the Examiner fell within the scope of the Challenged Claims.

Obviousness. The Challenged Claims would also have been obvious. The prior art demonstrates—and Dr. Albini confirms—monthly intravitreal injections for angiogenic eye disorders were known to be burdensome—both physically and financially. Skilled artisans were thus moving away from monthly dosing VEGF antagonists in favor of less frequent schedules. For example, Genentech—following the industry trend—had showed success with PRN dosing (after three fixed monthly injections) for LUCENTIS®. Accordingly, a skilled artisan would have (1) been highly motivated to combine such knowledge with the prior art disclosures that

VEGF Trap-Eye is a potent, high-affinity VEGF blocker[2], and (ii) reasonably expected success with the PRN dosing regimen based on the results from CLEAR-T-2. In fact, although unnecessary to prove obviousness, the prior art demonstrates *actual* success, further confirming that the Challenged Claims are invalid and the claimed dosing regimen unpatentable.

For the reasons set forth herein, Petitioner requests the Challenged Claims be cancelled.

III. MANDATORY NOTICES (37 C.F.R. § 42.8).

Pursuant to 37 C.F.R. §§ 42.8(a)(1) and 42.8(b), the following mandatory notices are provided as part of this Petition.

A. REAL PARTIES-IN-INTEREST (37 C.F.R. § 42.8(b)(1)).

Petitioner Apotex Inc. is the real party-in-interest. Additional real parties-in-interest are Apotex Corp., Apotex Pharmaceutical Holdings Inc. and Aposherm Delaware Holdings Corp. No other parties exercised or could have exercised control over this Petition; no other parties funded, directed and controlled this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48759-60 (Aug. 14, 2021).

[2] (Ex.1004, Holash; Ex.1005, Nguyen-2009; Ex.1006, Dixon; Ex.1007, Adis; Ex.1008, '173 patent; Ex.1009, '664 patent; *see* also Ex.1010, '758 patent (disclosing nucleotide and amino acid sequences for aflibercept)).

B. RELATED MATTERS (37 C.F.R. § 42.8(b)(2)).

Petitioner identifies *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, Case No. IPR2021-00881 (P.T.A.B.), filed May 5, 2021, and *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00880 (P.T.A.B.), filed May 5, 2021. To the best of Petitioner's knowledge, there are no other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding; nonetheless, out of an abundance of caution, Petitioner further identifies *Chengdu Kanghong Biotechnology Co. v. Regeneron Pharms., Inc.*, Case No. PGR2021-00035 (P.T.A.B.).

U.S. Patent Nos. 10,130,681 B2, 10,857,205 B2, 10,828,345 B2, and 10,888,601 B2; and U.S. Patent Application Nos. 17/072,417, 17/112,063, and 17/112,404 claim the benefit of the '069 patent filing date.

C. LEAD AND BACK-UP COUNSEL AND SERVICE INFORMATION (37 C.F.R. § 42.8(b)(3),(4)).

Petitioner identifies their lead and backup counsel below. A Power of Attorney is being filed concurrently herewith under 37 C.F.R. § 42.10(b).

Lead	Back-Up
Teresa Stanek Rea (Reg. No. 30,427) CROWELL & MORING LLP Intellectual Property Group 1001 Pennsylvania Avenue, N.W. Washington, DC 20004-2595 Telephone No.: (202) 624-2620 Facsimile No.: (202) 628-5116 TRea@Crowell.com	Deborah H. Yellin (Reg. No. 45,904) CROWELL & MORING LLP Intellectual Property Group 1001 Pennsylvania Avenue, N.W. Washington, DC 20004-2595 Telephone No.: (202) 624-2947 Facsimile No.: (202) 628-5116 DYellin@Crowell.com Shannon M. Lentz (Reg. No. 65,382) CROWELL & MORING LLP Intellectual Property Group 1001 Pennsylvania Avenue, N.W. Washington, DC 20004-2595 Telephone No.: (202) 624-2897 Facsimile No.: (202) 628-5116 SLentz@Crowell.com

Please direct all correspondence to lead and back-up counsel at the contact information above. Petitioner also consents to service by email at: TRea@Crowell.com, DYellin@Crowell.com, and SLentz@Crowell.com

IV. PAYMENT OF FEES UNDER 37 C.F.R. § 42.15(a) AND § 42.103

The required fees are submitted herewith. The undersigned representative of Petitioner hereby authorizes the Patent Office to charge any additional fees or credit any overpayment to Deposit Account No. 05-1323 (Customer ID No. 23911).

V. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a)).

Petitioner certifies that the '069 patent—which issued on June 6, 2017—is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging any claim of the '069 patent on the grounds identified herein. Neither Petitioner nor any other real-party-in-interest has filed a civil action challenging the validity, or been served with a complaint alleging infringement of the '069 patent, more than one year prior to this Petition's filing. *See Motorola Mobility LLC v. Arnouse*, No. IPR2013-00010, 2013 WL 12349001, *3 (P.T.A.B. Jan. 30, 2013).

VI. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW.

This Petition meets and exceeds the threshold required under 35 U.S.C. § 314(a). As explained below, for each ground, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the Challenged Claims.

VII. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED.

A. CHALLENGED CLAIMS.

Petitioner requests IPR of claims 1 and 8-12 of the '069 patent, and cancellation of these claims as unpatentable.

B. STATUTORY GROUNDS OF CHALLENGE.

Each of the following prior art references and/or combinations of references renders the Challenged Claims invalid:

Ground	35 U.S.C.	References	'069 patent Claims
1, **2**	§ 102	CLEAR-IT-2, as disclosed in either Heier-2009 or Dixon	1, 9-12
3	§ 102	Regeneron (30-April-2009)	1, 9-12
4	§ 102 and/or § 103	VIEW1/VIEW2, as disclosed in Dixon	1, 8-12
5	§ 103	Heier-2009, in view of Mitchell or Dixon, and optionally, the '758 patent or Dix	1, 8-12

Petitioner's full statement of the reasons for the relief requested is set forth in greater detail below, and in the supporting declarations of Drs. Albini and Gerritsen.

VIII. OVERVIEW OF THE '069 PATENT AND PROSECUTION HISTORY

A. THE '069 PATENT.[3]

The '069 patent claims a known dosing regimen for treating angiogenic eye disorders—including AMD—that amounts to administering a single initial dose of a VEGF antagonist (VEGF Trap-Eye)[4], followed by one or more "secondary doses"

[3] Solely for purposes of this IPR, Petitioner assumes a January 13, 2011 priority date.

[4] Vascular endothelial growth factor or VEGF is a "naturally occurring glycoprotein

administered two to four weeks after the immediately preceding dose, followed by one or more "tertiary doses" administered on a PRN basis. The specification establishes that angiogenic eye disorders, such as AMD, diabetic macular edema ("DME"), and retinal vein occlusion ("RVO"), were known to be effectively treated through the inhibition of vascular endothelial growth factor ("VEGF"). (Ex.1001, '069 patent, 1:24-53).

The specification also sets forth AMD dosing regimens employing PRN dosing disclosed in the prior art before the '069 patent application was filed, including the Phase 2 monthly loading dose/PRN regimen and the Phase 3 loading dose/every-eight-week regimen, in which patients received PRN injections in the second year. (*Id.*, 8:19-49 (Example 2, disclosing CLEAR-IT-2); *id.*, 9:11-13:49 (Example 4)).

However, Petitioner reserves all rights to challenge the extent to which Regeneron asserts application of pre-AIA standards of patentability. The '069 patent is subject to the AIA given the inclusion of new matter in the Continuation-In-Part Application No. 13/940,370, filed July 12, 2013.

---

in the body that acts as a growth factor for endothelial cells." (Ex.1011, Semeraro, 711). Early research linked activity of VEGF-A to the development of ocular diseases such as neovascular AMD. (*Id.*).

Example 2, like the prior art, lists the five treatment arms in the CLEAR-IT-2 trial, including administering VEGF Trap-Eye via intravitreal injection to AMD patients at a fixed interval (e.g., four-week) for the first 12 weeks. (*Id.*, 8:26-33). After 12 weeks, subjects "were evaluated every 4 weeks for 9 months, during which additional doses were administered based on pre-specified criteria." (*Id.*, 8:29-33). In other words, subjects assigned to the "4-week" fixed interval groups received four monthly doses, followed by PRN dosing.[5]

Example 4 describes parallel Phase 3 clinical trials carried out to investigate the use of VEGF Trap-Eye to treat AMD: the VIEW1/VIEW2 trials.[6] (Ex.1001, '069 patent, 9:11-13:49). Example 4 discloses that patients enrolled in VIEW1/VIEW2 were assigned to one of four treatment arms employing varying dosing regimens for the first year of the study (*id.*, 9:45-58); whereas the second year reverted to PRN dosing for all subjects (*id.*, 9:63-10:13 ("During the second year of the study, subjects will be evaluated every 4 weeks and will receive [intravitreal] injection of study drug

[5] The CLEAR-IT-2 PRN dosing regimen was disclosed in the prior art by at least 2008. (Ex.1012, Regeneron (28-April-2008), 1).

[6] The VIEW1/VIEW2 trials were fully disclosed in the prior art as early as 2008. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1014, NCT-795, 8; Ex.1015, NCT-377, 6).

at intervals determined by specific dosing criteria.")). Most notably, Arm-2Q8 involved "2 mg VEGFT administered every 4 weeks to week 8 and then every 8 weeks." (*Id.*, 9:45-58). That is, VEGF Trap-Eye was administered in three monthly doses, followed by eight-week dosing intervals in the first year, followed by PRN dosing in the second year.

B. PROSECUTION HISTORY.

During prosecution, Regeneron made several arguments against the Examiner's rejections over Regeneron's Monthly-Dosing Patents[7] for obviousness-type-double-patenting ("OTDP"). First, Regeneron argued that its Monthly-Dosing-Patents did not disclose the exact regimen of the PRN dosing claims. (Ex.1017, '069 FH, 1/30/2017 Amendment, 5). Second, Regeneron represented that once-per-month dosing was the standard of care and alleged the less frequent administration under the Challenged Claims produced unexpected results. (*Id.*, 6-8).

Third, and most notably, Regeneron presented the VIEW1/VIEW2 results—published in Heier-2012 (Ex.1018)—as purported evidence of surprising and unexpected results, in attempt to support the Challenged Claims' patentability. (*Id.*,

[7] Regeneron's "Monthly-Dosing Patents" refers to U.S. Patent Nos. 7,303,746; 7,303,747; 7,306,799; and 7,521,049; which generally disclose doses separated by at least two weeks. (*See* Ex.1016, Monthly-Dosing Patents).

6-8). Specifically, Regeneron asserted:

> [T]he results show that the treatment groups which were compared with the monthly treatment groups surprisingly did not obtain an inferior result. As such, the PRN treatment protocol as encompassed by the presently pending independent claim 1 achieves results which are as good or better than the results obtained with monthly treatment.

(*Id.*). In other words, Regeneron told the Examiner that the VIEW1/VIEW2, every-eight-week dosing regimen represents a "PRN treatment protocol." (Ex.1017, '069 FH, 1/30/2017 Amendment, 6 ("Heier et al. paper shows results of a treatment protocol *of the type claimed*.") (emphasis added)).

As purportedly further support, Regeneron stated that Heier-2012 echoes the '069 patent's conclusion that administration "at a ***frequency of once every 8 weeks***, following a single initial dose and two secondary doses administered four weeks apart, resulted in significant prevention of moderate or severe vision loss or improvements in visual acuity." (*Id.*, 7-8 (emphasis added); *id.*, 8 (alleging "the ***claimed*** treatment protocol provides enormous advantages to patients" based on outcomes observed in Heier-2012 for the every-two-month VIEW1/VIEW2 dosing

regimen) (emphasis added)).[8]

Regeneron lastly argued that Example 5 "illustrates an administration regimen encompassed by [issued] claim 1 (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered as needed (PRN)) for the effective treatment of diabetic macular edema." (*Id.*, 7).

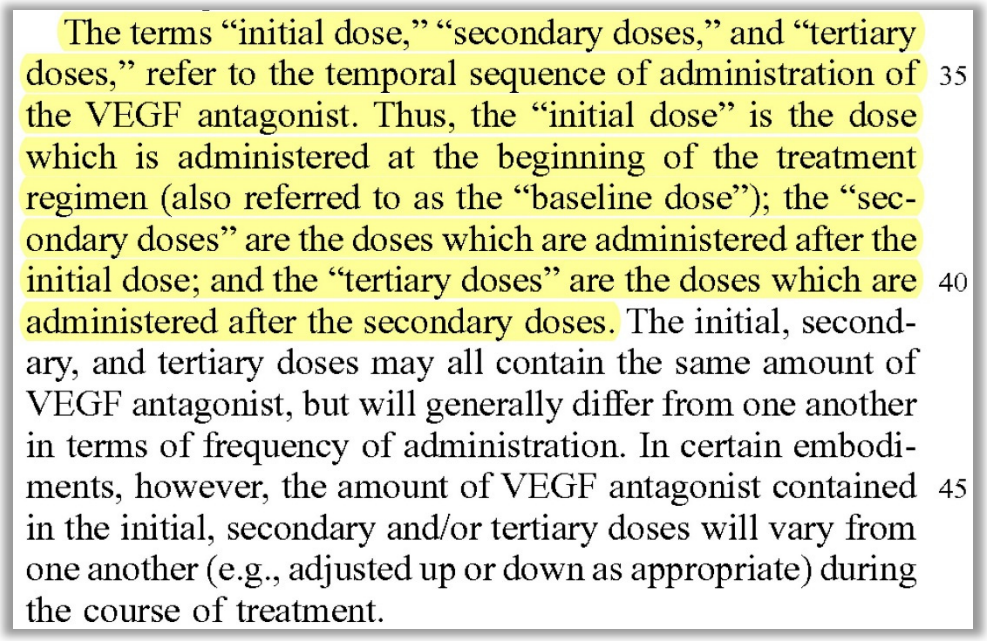
IX. CLAIM CONSTRUCTION (37 C.F.R. § 42.104(b)(3)).

In accordance with 37 C.F.R. § 42.100(b), the Challenged Claims must be "construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b)," i.e., the *Phillips* standard. 83 Fed. Reg. 197, 51340-51359 (Oct. 11, 2018); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). Here, Petitioner and expert declarant, Dr. Albini, have applied this standard.

A. "INITIAL DOSE," "SECONDARY DOSE," AND "TERTIARY DOSE."

The Challenged Claims recite the phrases "initial dose," "secondary dose," and "tertiary dose." A skilled artisan would understand each as expressly defined in the '069 patent specification:

[8] Regeneron never informed the Examiner that the VIEW dosing regimen in Heier-2012 was the subject of numerous pre-2011 public disclosures (discussed in greater detail below).



The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist, but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist contained in the initial, secondary and/or tertiary doses will vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment.

(Ex.1001, '069 patent, 3:34-48 (emphasis added)). The specification further explains that "the immediately preceding dose" means "in a sequence of multiple administrations, the dose of VEGF antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses." (*Id.*, 3:54-59; *see also* Ex.1002, Albini, ¶ 40). Petitioner proposes that each claim term be construed consistent with these express definitions: "initial dose" means "the dose which is administered at the beginning of the treatment regimen"; "secondary dose(s)" means "the dose(s) which are administered after the initial dose"; and "tertiary dose(s)" means "the dose(s) which are administered after the secondary dose(s)."

1. Regeneron's contradictory construction for "tertiary dose," if presented here, must be rejected.

To the extent Regeneron proposes the same construction for "tertiary dose" that it has in the '345 Patent PGR—i.e., "dose(s) that maintain(s) a therapeutic effect throughout the course of treatment," (PO Preliminary Response, *Chengdu Kanghong Biotechnology Co. v. Regeneron Pharms., Inc.*, No. PGR2021-00035, Paper 6, 9 (P.T.A.B. Apr. 15, 2021) ("'345 Patent PGR"))—it should be rejected for at least the following reasons.

First and foremost, as described above, the '069 patent specification recites an *express* definition that provides the patentees' intended meaning to the claims:

> the "tertiary doses" are the doses which are 40
> administered after the secondary doses.

(Ex.1001, '069 patent, 3:40-41 (emphasis added)). The term is "set off by quotation marks," which "[is] often a strong indication that what follows is a definition"—"the patentee must be bound by the express definition." *Sinorgchem Co., Shandong Int'l Trade Comm'n*, 511 F.3d 1132, 1136 (Fed. Cir. 2007). In other words, "tertiary dose" is "clearly, deliberately, and precisely defined," (*id.*), in the '069 patent—nothing more is needed and there is no basis for straying from that express definition.

Second, Regeneron's proposed construction is unsupported and the intrinsic record does not suggest reading-in limitations. *Phillips*, 415 F.3d at 1323 (reaffirming the need "to avoid the danger of reading limitations from the

specification into the claim"). For example, Regeneron relies exclusively on column 2 as purported support for its narrowed construction ('345 Patent PGR, 11), but that specification passage only describes a single embodiment—i.e., bimonthly dosing—and is not even relevant to the "as-needed/*pro re nata* (PRN)" dosing regimen(s) of the Challenged Claims. (Ex.1001, '069 patent, 2:14-16 ("***[E]ach*** tertiary dose is administered ***at least 8 weeks after*** the immediately preceding dose.") (emphasis added)).[9] By comparison, the *express* definition recited in the specification (i.e.,

[9] The '338 patent purportedly claims this dosing regimen, with bimonthly doses as the "tertiary doses." However, Regeneron's proposed construction for "tertiary doses" is in conflict with the language of the '338 patent claims, which require "tertiary doses" administered "at least 8 weeks after the immediately preceding dose" irrespective of whether the injection "maintain[s] a therapeutic effect." (*See* Ex.1019, '338 patent, 23:2-18, *id.*, 24:24-25 (claims 1 and 17)). Consequently, the '338 patent—which derives from the same parent application as the '069 patent and the Chengdu-challenged '345 patent—would improperly require a different construction of "tertiary dose" for those claims to have meaning, further illustrating the extent to which Regeneron's proposed construction, if presented in this IPR, would inject indefiniteness into the claim. *Samsung Elecs. Co. v. Elm 3DS Innovations, LLC,* 925 F.3d 1373, 1378 (Fed. Cir. 2019) ("Where multiple patents

"doses which are administered after the secondary doses") provides the exact temporal and sequential distinction from the other doses in the regimen that the patent drafters intended. (Ex.1001, '069 patent, 3:34-36 ("The terms . . . refer to the temporal sequence of administration.")). *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so."). No further construction is necessary. *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998) ("When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term.").

Third, Regeneron's proposal improperly injects ambiguity and indefiniteness where there is none. *Ruckus Wireless, Inc. v. Innovative Wireless Sols., LLC*, 824 F.3d 999, 1004 (Fed. Cir. 2016) (rejecting a construction encompassing subject matter that would render the claims invalid under § 112). Regeneron's proposed construction, itself, requires construction—i.e., "maintain," "therapeutic effect," and "throughout the course of treatment" lack definition and plain and ordinary meanings. A skilled artisan is therefore left wondering what Regeneron's

---

derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents.")

construction is supposed to mean, as well as what metrics one is supposed to use to assess each imported limitation. Moreover, Regeneron's added language renders the "as-needed/pro re nata" element of the Challenged Claims—which a skilled artisan would already understand as administration to maintain a therapeutic benefit—duplicative and meaningless. *Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396 (Fed. Cir. 2004) ("[I]nterpretations that render some portion of the claim language superfluous are disfavored.").

Finally, Regeneron notably ignores "initial" and "secondary." Consequently, a skilled artisan, under Regeneron's proposal, is uncertain whether those terms carry "therapeutic effect" limitations as well, or whether the specification's express definitions apply—adding further uncertainty and ambiguity to the Challenged Claims. Petitioner's proposal to apply the express definitions for all three terms, on the other hand, is clear to a skilled artisan and free of the ambiguity of Regeneron's proposed construction.

B. "4 WEEKS" AND "PRO RE NATA (PRN)."

"4 weeks." Challenged claims 1, 2, and 8 recite the term "4 weeks." A skilled artisan would understand "4 weeks" as "monthly" administration. (Ex.1001, '069 patent, 7:58-59 ("'[M]onthly' dosing is equivalent to dosing once every four weeks."); *id.*, 14:47-48 (patients received "monthly injections," which "means patients who received... injections once every four weeks"); Ex.1002, Albini, ¶ 41).

"Pro Re Nata (PRN)." Independent claim 1 recites the term "pro re nata (PRN)," which is expressly defined in the claim language as "as-needed." (Ex.1001, '069 patent, 21:50-51 ("administered on an as-needed/pro re nata (PRN) basis")). The specification is consistent with the claim language and with the term's use among skilled artisans. (Ex.1001, '069 patent, 14:43 ("as-needed (PRN"); 15:43-48 ("administered pro re nata (PRN) based on visual and/or anatomical outcomes"); 16:9-49; Ex.1002, Albini, ¶ 43).

C. "VEGFR1 COMPONENT," "VEGFR2 COMPONENT," AND THE "MULTIMERIZATION COMPONENT."

Claim 1 of the '069 patent recites that the "VEGF antagonist" comprises a "VEGFR1 component," a "VEGFR2 component," and a "multimerization component." According to the '069 patent, these terms all refer to separate amino acid domains of "SEQ ID NO:2." A skilled artisan would understand these terms to collectively refer to aflibercept (i.e., VEGF Trap, VEGF Trap-Eye, or VEGFR1R2-FcΔC1(a)). (Ex.1001, '069 patent, 2:34-38; Ex.1002, Albini, ¶ 39).

D. "TREATING."

1. The "method for treating" element of the preamble is <u>not</u> a limitation on the Challenged Claims, and therefore, does not require construction.

The "method for treating" element of independent claim 1 is "merely a statement of purpose or intended use" for the claimed dosing regimen(s) and is non-limiting. *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375

(Fed. Cir. 2001); *Vizio, Inc. v. Int'l Trade Comm'n*, 605 F.3d 1330, 1340-41 (Fed. Cir. 2010); *Arctic Cat Inc. v. GEP Power Prods., Inc.*, 919 F.3d 1320, 1327 (Fed. Cir. 2019) ("as a general rule preamble language is not treated as limiting")). Indeed, "method for treating"—like the "method" preamble in *Bio-Rad*—neither provides antecedent basis for any other claim element[10] nor gives life, meaning or vitality to the claimed dosing regimen, and thus, it is not a limitation. *Bio-Rad Lab'ys, Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1371 (Fed. Cir. 2020) (citing *TomTom, Inc. v. Adolph*, 790 F.3d 1315, 1322-25 (Fed. Cir. 2015)) ("In *TomTom* . . . [t]he two-part preamble of the asserted claim recited: '[1] [a] method for generating and updating data [2] for use in a destination tracking system of at least one mobile unit comprising We held that the first part of the preamble, 'method for generating and updating data,' was not limiting and did not provide an antecedent basis for any claim terms. We also found that the term did not recite essential structure or steps, or give necessary life, meaning, and vitality to the claim; rather, it stated 'a purpose or intended use.'" (citations omitted)); *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (preamble was non-limiting where it "does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims"). Nothing in

[10] "Treating" (or any form of "treat") appears nowhere else in any of the claims.

the intrinsic record here suggests otherwise. For example, there is no evidence that Regeneron asserted the "method for treating" preamble to traverse any Examiner rejections. Instead, Regeneron relied on the dosing frequencies required in the Challenged Claims to purportedly distinguish the prior art, "standard of care." (Ex.1017, '069 FH, 1/30/2017 Amendment, 5-6).

Moreover, Regeneron is foreclosed by Federal Circuit precedent from arguing that its reliance on alleged "unexpected results" during prosecution demonstrates that efficacy is a necessary feature of the claimed method. *Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1136-37 (Fed. Cir. 2006) (en banc) (holding that patentee's reliance on its "surprising discovery" of the four-fold dosage range to distinguish its oxycodone formulation from the prior art did not make the four-fold range a necessary feature of the claimed formulations). The Board has also rejected similar arguments. *Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, No. IPR2016-00712, 2016 WL 5753968, *5 (P.T.A.B. Sept. 22, 2016) (holding that "method of treating a patient" preamble was non-limiting despite patentee's reliance on "surprising and unexpected" clinical results of efficacy to distinguish the claimed invention from the prior art).

For these reasons, Petitioner submits that the preamble is non-limiting and no construction of "treating" is necessary to ascertain the scope of the Challenged Claims.

2. Regeneron's anticipated argument that the "method for treating" preamble is a positive limitation should be rejected.

In the '345 Patent PGR, Regeneron has asserted that an analogous "method for treating" element to the claim preamble is a positive limitation requiring a therapeutically effective method of treatment. ('345 Patent PGR, 7-9). To the extent Regeneron raises the same argument here, it should be rejected. First, the "method for treating" preamble has no bearing on the dosing steps in the Challenged Claims, because "the steps . . . are performed in the same way regardless whether or not the patient experiences" treatment of their angiogenic eye disorder. *Bristol-Myers*, 246 F.3d at 1375. In other words, the preamble is merely a statement of the *intended* purpose for the claimed regimen, and therefore, is not a limitation. *Id.*; *Copaxone*, 906 F.3d at 1022-23.

Second, as stated above, "method for treating" provides no antecedent basis for any other claim element, and any argument that the claim terms "the patient" and "angiogenic eye disorders" find their respective meaning in the preamble is meritless. Like in *Copaxone*, these terms do not "change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims." *Copaxone*, 906 F.3d at 1023. Instead, the claimed dosing regimen stays the same. Consequently, neither the "method for treating" element nor the "angiogenic eye disorder in a patient" element in the two-part preamble rise to the level of a positive claim limitation.

Third, even if the Board finds the preamble limiting, the claimed method is not *required*—as Regeneron argues—to be therapeutically effective. Instead, the preamble is "a statement of the intentional purpose for which the method must be performed." *GlaxoSmithKline LLC v. Glenmark Pharms., Inc.*, No. 14-877-LPS-CJB, 2016 WL 3186657, at *7 (D. Del. June 3, 2016). Therefore, to anticipate the claims, it is enough that one's "intentional purpose" is to treat an angiogenic eye disorder—showing actual therapeutic effectiveness is not required.

3. If construed to be a limitation, the preamble's plain and ordinary meaning—which does not provide any specific efficacy requirement—must govern.

If the Board determines that the claim language requires construction, or that the preamble is a limitation, the patent does not provide a definition or metric for what constitutes "treating" an angiogenic eye disorder within the context of the Challenged Claims. Given this absence of lexicography, a skilled artisan would apply the term's plain and ordinary meaning: administering a therapeutic to a patient, without any specific efficacy requirement. (Ex.1002, Albini, ¶ 42).

In the event Regeneron attempts to equate "efficacy" with "treating" (which, at the outset, is impermissible under Federal Circuit precedent, *see Phillips*, 415 F.3d at 1323), the Challenged Claims are still unpatentable for the reasons set forth herein. Specifically, "efficacy" in the context of the '069 patent only requires that the patient exhibit a loss of fifteen or fewer letters on the Early Treatment Diabetic Retinopathy

Study ("ETDRS") visual acuity chart within 104 weeks of treatment initiation. (*See, e.g.*, Ex.1001, '069 patent, 7:18-34). Even the "certain embodiments" efficacy metric requires only a gain of one or more ETDRS letters within 104 weeks. Applied to the claims, efficacy far exceeding this *de minimis* level were indisputably disclosed in prior art using VEGF Trap-Eye dosing regimens that involved fewer doses than the every-8-week regimen. (*See, e.g.*, Ex.1020, Heier- 2009, 45 (reporting mean improvements in BCVA of 9.0 letters from baseline after "three monthly doses of 2.0 mg followed by as-needed dosing"); *id.* (reporting "patients received a mean 3.5 injections" over 15-month PRN dosing phase)). To the extent efficacy is required, the "method for treating" element of the preamble is also inherently anticipated by the prior art disclosing the exact method claimed in the '069 patent. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005); *King Pharms., Inc. v. Eon Lab'ys, Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010).

X. PERSON OF ORDINARY SKILL IN THE ART.

A person of ordinary skill in the art (referred to herein as a "skilled artisan") is presumed to be aware of all pertinent art, think along the lines of conventional wisdom, and possess common sense and ordinary creativity in the pertinent field. A skilled artisan here would have: (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 in this Petition. 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 angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists. (Ex.1002, Albini, ¶¶ 26-28).

XI. THE SCOPE AND CONTENT OF THE PRIOR ART.

The publications below reflect invalidating disclosures of the claimed method(s), together with knowledge that skilled artisans would bring to bear in reading the prior art at the time, i.e., January 13, 2011. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367-68 (Fed. Cir. 2015). As established in *KSR*, the knowledge of a skilled artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-22 (2007).

A. VEGF TRAP-EYE/AFLIBERCEPT BACKGROUND.

As an initial matter, aflibercept—also known as VEGF Trap, VEGF Trap-Eye, VEGF-Trap$_{R1R2}$, and AVE0005—is an engineered prior art fusion protein consisting of domain 2 of the human VEGF receptor 1 (VEGFR1); domain 3 of the

human VEGF receptor 2 (VEGFR2); fused to the Fc portion of human IgG_1. (Ex.1004, Holash, 11394 (Fig.1A); Ex.1002, Albini, ¶¶ 63-69). Aflibercept, VEGF Trap, and VEGF Trap-Eye are simply different names for the same molecule. (Ex.1006, Dixon, 1575 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure"); Ex.1021, 2009 10-Q, 20 ("VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications."); *see also id.*, 27; Ex.1007, Adis, 261 ("Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap(R1R2), VEGF Trap-Eye")).

The coding sequence for VEGF Trap-Eye/aflibercept was widely disclosed in the prior art as well. (Ex.1022, '757 patent, SEQ ID NO:15, SEQ ID NO:16, Fig.24A-C; Ex.1010, '758 patent, SEQ ID NO:15, SEQ ID NO:16, Fig.24A-C; Ex.1023, '959 patent, Fig.24A-C; Ex.1002, Albini, ¶ 39). While the identity of VEGF Trap-Eye/aflibercept would have been readily apparent from the prior art disclosures (*see* Ex.1007, Adis, 261-63 (conveying knowledge of the molecular structure); Ex.1006, Dixon, 1575 (same)), Regeneron also confirmed the information in a Patent Term Extension application, explaining that aflibercept is a fusion protein consisting of domain 2 of Flt1, domain 3 of Flk1, and an Fc portion of human IgG1, the amino acid sequence of which is set forth in SEQ ID NO:16 and Fig.24A-C of the '758 patent. (Ex.1024, '758 FH, 12/22/2011 PTE, 2, 6-7). Thus, the molecular structure and sequence for aflibercept was not only known to skilled

artisans, and expressly disclosed in the prior art, but also would have been an inherent aspect of each of the references discussed below that disclose VEGF Trap-Eye/aflibercept. *See Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380 (Fed. Cir. 2002).

VEGF Trap-Eye was developed to target VEGF-related angiogenic disorders, including eye disorders, such as AMD, DME, and RVO. (Ex.1002, Albini, ¶¶ 44-52, 63-69). Earlier generation therapeutics targeted specifically at blocking VEGF included ranibizumab (LUCENTIS®) and bevacizumab (AVASTIN®), both monoclonal antibodies, which bind to, and thus inhibit the activity of VEGF-A. (Ex.1002, Albini, ¶¶ 54-58). However, the FDA-approved monthly dosing regimen for ranibizumab was costly and inconvenient, leading researchers to: (1) investigate less-frequent dosing regimens; and (2) focus on new drugs with extended duration of action. (Ex.1006, Dixon, 1574; Ex.1002, Albini, ¶¶ 58-62; Ex.1025, Engelbert-2010, 1369; Ex.1026, Engelbert-2009, 1425, 1429; Ex.1027, Spaide, 298). The potential for VEGF Trap-Eye to "block[] all isoforms of VEGF-A and placental growth factors-1 and -2," coupled with the need for alternative dosing schedules that might reduce the burden of monthly injections, led to the commercial development and testing of Regeneron's VEGF Trap-Eye. (Ex.1006, Dixon, 1573). At the time, LUCENTIS® approved indications overlapped those Regeneron was exploring for EYLEA®. Both are VEGF antagonists.

VEGF Trap-Eye was placed into AMD clinical studies in the mid-2000's, entering Phase 2 testing on or around 2007. The Phase 2 regimen involved four monthly loading doses, followed by PRN dosing. (Ex.1006, Dixon, 1573-74; Ex.1018, Heier-2012, 2573; Ex.1012, Regeneron (28-April-2008), 1). In August 2007, Phase 3 testing began. (Ex.1006, Dixon, 1576; Ex.1002, Albini, ¶ 70; Ex.1007, Adis, 263-64; Ex.1013, Regeneron (8-May-2008), 1; Ex.1014, NCT-795, 8; Ex.1015, NCT-377, 6).

VEGF Trap-Eye was also used in clinical studies involving central retinal vein occlusion ("CRVO"). In 2009, Regeneron announced Phase 3 programs, which involved six monthly injections followed by PRN dosing. (Ex.1028, Regeneron (30-April-2009), 1; Ex.1029, NCT-973, 3-5; Ex.1021, 2009 10-Q, 20, 27; Ex.1002, Albini, ¶ 70).

B. PETITIONER'S PRIOR ART REFERENCES.[11]

Because much of the prior art relates to Regeneron's VEGF Trap-Eye clinical trials, the following summary table is provided:

[11] The asserted prior art references all qualify as publications that were available to—and indeed cited by—interested, skilled artisans before January 13, 2011. (Ex.1003, Gerritsen, ¶¶ 52, 60, 66, 72, 76-78, 85, 93, 95; Ex.1006, Dixon, 1579 (Bibliography Nos. 46-47); Ex.1007, Adis, 268 (Ref. Nos. 10-14)).

Trial	Name	Prior Art Disclosures	Dosage Regimen
Phase 1 (AMD)	CLEAR-IT-1	Dixon; Nguyen	Single intravitreal dose (0.5, 2, and 4 mg doses)
Phase 2 (AMD)	CLEAR-IT-2	Dixon; Adis; Regeneron (28-April- 2008); Heier-2009	Four monthly doses (0.5, 2, and 4 mg doses); PRN thereafter
Phase 3 (AMD)	VIEW-1/ VIEW- 2	Dixon; Adis; Regeneron (8- May-2008); NCT-795; NCT-377	Three monthly doses, followed by injections every eight weeks (0.5 and 2 mg doses); PRN dosing the second year
Phase 3 (CRVO)	GALILEO; COPERNICUS	Regeneron (30-April- 2009); NCT-973	Six monthly doses (2 mg); PRN thereafter
Phase 2 (DME)	DA VINCI	Regeneron (18-February-2010)	Three monthly doses (2 mg); PRN thereafter

(Ex.1002, Albini, ¶¶ 70, 72-73).

The following summarizes Genentech's various ranibizumab trials exploring alternative dosing schedules that reduced injection frequency—all relevant to the Challenged Claims:

Dosing Regimen	Trial[12] (Disease)
Monthly	MARINA (AMD)
	ANCHOR (AMD)
Quarterly after three monthly injections	PIER (AMD)
	EXCITE (AMD)
PRN after three monthly injections	PrONTO (AMD)
	SAILOR (AMD)
	SUSTAIN (AMD)
	RESOLVE (DME)

(Ex.1002, Albini, ¶ 71).

[12] *See* Ex.1030, Mitchell, 9-10); Ex.1031, Massin, 55 (RESOLVE study)).

1. Dixon (Ex.1006).

Dixon published in 2009 and thus constitutes prior art under 35 U.S.C. § 102. Dixon was not cited by the Examiner. Dixon reviews VEGF Trap-Eye in treating AMD. Dixon discusses, *inter alia*, the vitreoretinal market and the VEGF Trap-Eye molecular structure, as well as the CLEAR-IT-1, CLEAR-IT-2, and VIEW1/VIEW2 clinical trials. (Ex.1002, Albini, ¶ 74).

Dixon discloses that the "time and financial burden of monthly injections" led researchers to "examine the efficacy of alternative dosing schedules." (Ex.1006, Dixon, 1574-77 (citing, e.g., PIER and PrONTO studies). Based upon the positive results in the ranibizumab PrONTO study (three monthly injections followed by PRN dosing), Dixon concludes that "it may be possible to extend the time between injections if the patient is frequently monitored." (*Id.*, 1574, 1577; Ex.1002, Albini, ¶¶ 76-77).

Dixon specifically identifies the "desirab[ility]" of "decreased dosing intervals," (Ex.1006, Dixon, 1577), as the motivation for the "development of new drugs for neovascular AMD . . . focused on both improving efficacy and extending duration of action," (*id.*, 1574; Ex.1002, Albini, ¶ 78). To that end, Dixon calls VEGF Trap-Eye "the most promising anti-VEGF investigational drug" in Phase 3 trials. (Ex.1006, Dixon, 1577 (referring to VIEW1/VIEW2)).

Dixon discloses the VEGF Trap-Eye clinical trials, including their dosing

regimens, which implemented the dosing intervals already successful with ranibizumab (LUCENTIS®). Dixon discloses the promising results from CLEAR-IT-2, which included four monthly doses (at weeks 0, 4, 8 and 12) followed by PRN administration. (*Id.*, 1576). Dixon reports that CLEAR-IT-2 subjects treated with that regimen exhibited mean improvement in visual acuity of nine letters and a mean decrease in retinal thickness of 143 μm. (*Id.*; Ex.1002, Albini, ¶¶ 79-80). Dixon further reports that "patients dosed at 2.0 mg during the initial monthly dosing period required 1.6 injections on average during the p.r.n. dosing phase." (Ex.1006, Dixon, 1577).

Dixon also discloses the VIEW1/VIEW2 dosing regimens. (*Id.*, 1573, 1575-76, 1579 (Bibliography Nos. 46-47) (citing ClinicalTrials.gov reports); Ex.1002, Albini, ¶¶ 81-82; Ex.1003, Gerritsen, ¶ 93). Dixon discloses that some VIEW1/VIEW2 patients were to receive intravitreal "2.0 mg [VEGF Trap-Eye] at an 8 week dosing interval (following three monthly doses)," (Ex.1006, Dixon, 1576) which can be illustrated as follows:

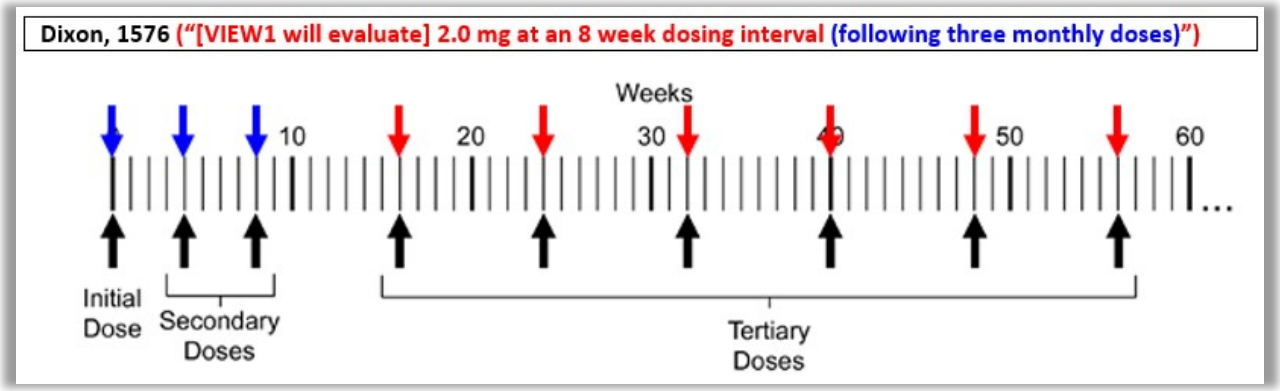


Figure 1. (Modified from Fig.1 of the '069 patent).

After the first year, all patients would "enter a second year of p.r.n. dosing evaluation." (Ex.1006, Dixon, 1576).

Numerous other prior art references disclose Regeneron's CLEAR-IT-2 and/or VIEW1/VIEW2 study details. (*See, e.g.,* Ex.1007, Adis, 262-63; Ex.1013, Regeneron (8-May-2008), 1; Ex.1014, NCT-795, 3-8; Ex.1015, NCT-377, 3-7; Ex.1002, Albini, ¶¶ 83-89).

2. Regeneron (28-April-2008) (Ex.1012).

Regeneron (28-April-2008) published on April 28, 2008, and thus constitutes prior art under 35 U.S.C. § 102.[13] To Petitioner's knowledge, Regeneron (28-April-2008) was neither submitted nor cited during prosecution, and thus never considered

[13] Bayer's corresponding press release was also publicly available to skilled artisans before January 13, 2011. (Ex.1032, Bayer (8-May-2008), 1; Ex.1007, Adis, 268 (Ref. No. 13); Ex.1003, Gerritsen, ¶¶ 76-78; Ex.1002, Albini, ¶ 87).

by the Examiner. (Ex.1001, '069 patent, References Cited).

Regeneron (28-April-2008) discloses the CLEAR-IT-2 and VIEW regimens encompassed by the Challenged Claims. For example, Regeneron (28-April-2008) explains that patients in CLEAR-IT-2 received monthly fixed dosing through 12 weeks, followed by PRN administration. (Ex.1012, Regeneron (28-April-2008), 1; Ex.1002, Albini, ¶¶ 90-91). Regeneron also announced the dosing format for VIEW1/VIEW2 as three fixed monthly doses followed by every-eight-week dosing through the first year with PRN dosing in the second year. (Ex.1012, Regeneron (28-April-2008), 1; Ex.1013, Regeneron (8-May-2008), 1).

Regeneron (28-April-2008) also reports gains in visual acuity (10.1 letters) and decreases in retinal thickness (162 μm) after 32 weeks PRN dosing, maintaining the improvements seen after the 12 week loading dose phase. (Ex.1012, Regeneron (28-April-2008), 1; Ex.1002, Albini, ¶¶ 91-93). Regeneron (28-April-2008) reports Regeneron's confidence in successfully dosing "at a frequency less than once monthly," as demonstrated in its Phase 3, every-eight-week regimens. (Ex.1012, Regeneron (28-April-2008), 1-2).

3. Heier-2009 (Ex.1020).

Heier-2009, published in 2009 and thus constitutes prior art under 35 U.S.C. § 102.To Petitioner's knowledge, Heier-2009 was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, '069

patent, References Cited).

Heier-2009 discloses CLEAR-IT-2. (Ex.1020, Heier-2009, 44-45). Specifically, Heier-2009 describes the two treatment arms: (i) three monthly intravitreal injections followed by PRN; or (ii) quarterly intravitreal injections followed by PRN. (*Id.*, 45). Both arms included a 2.0 mg dosage strength. (*Id.*; Ex.1002, Albini, ¶¶ 94-95).

Heier-2009 reports that "[p]atients who received three monthly doses of 2.0 mg followed by as-needed dosing achieved mean improvements in BCVA of 9.0 letters from baseline"; "mean decreases in retinal thickness vs baseline"; and "a reduction in the size of the total active choroidal neovascular membrane." (Ex.1020, Heier-2009, 45; Ex.1002, Albini, ¶ 96).

Heier-2009 further discloses a six-month extension for CLEAR-IT-2, wherein 117 patients received additional PRN dosing (2.0 mg, VEGF Trap-Eye). (Ex.1020, Heier-2009, 45). These patients achieved BCVA improvement of 7.1 letters compared to baseline. (*Id.*, ("[patients with AMD] achieved and maintained significant improvement in BCVA for 18 months with initial fixed dosing followed by 15 months of as-needed administration."); Ex.1002, Albini, ¶¶ 97-99).

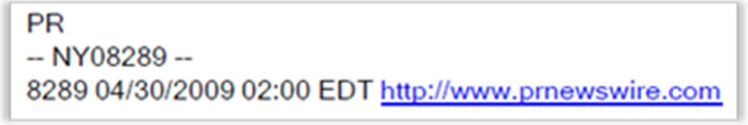
4. Regeneron (30-April-2009) (Ex.1028).

Regeneron (30-April-2009) published April 30, 2009, and thus constitutes

prior art under 35 U.S.C. § 102.[14] To Petitioner's knowledge, Regeneron (30-April-2009) was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, '069 patent, References Cited).

Regeneron (30-April-2009) reports Regeneron's development program for VEGF Trap-Eye to include CRVO—specifically, a Phase 3 program consisting of two one-year studies wherein patients receive six monthly injections, followed by six months of PRN dosing. (Ex.1028, Regeneron (30-April-2009), 1; Ex.1029, NCT-973, 3-5; Ex.1002, Albini, ¶¶ 100-01). The first was named "COPERNICUS" (Controlled Phase 3 Evaluation of Repeated Intravitreal administration of VEGF Trap-Eye In CRVO: Utility and Safety); and the second—led by Bayer—was named "GALILEO" (General Assessment Limiting Infiltration of Exudates in CRVO with VEGF Trap-Eye). (Ex.1028, Regeneron (30-April-2009), 1; Ex.1029, NCT-973, 3-5).

[14] Regeneron (30-April-2009) was publicly available to skilled artisans long before 2011. (Ex.1003, Gerritsen, ¶¶ 61-66; *see* supra note 12). More specifically, Regeneron (30-April-2009) is date stamped as follows:



(Ex.1028, Regeneron (30-April-2009), 2; Ex.1002, Albini, ¶ 102).

5. The ’758 patent (Ex.1010).

The ’758 patent issued on May 20, 2008, and thus constitutes prior art under 35 U.S.C. § 102.

The ’758 patent discloses “[m]odified chimeric polypeptides with improved pharmacokinetics,” including, *inter alia*, the VEGF $Trap_{R1R2}$ (i.e., VEGF Trap-Eye/aflibercept) fusion protein. (Ex.1010, ’758 patent, Abstract; *id.*, 19:15-17; *id.*, 29:39-56). The aflibercept sequence is disclosed in Figures 24A-C. (*Compare* Ex.1001, ’069 patent, SEQ ID NO:1 & SEQ ID NO:2, *with* Ex.1010, ’758 patent, Fig.24A-C, SEQ ID NO:15 & SEQ ID NO:16; *see also* Ex.1024, ’758 FH, 12/22/2011 PTE, 2, 6-7; Ex.1002, Albini, ¶¶ 39, 110-11; Ex.1082; Ex. 1083).

The ’758 patent also teaches that aflibercept may be useful for treating eye disorders such as AMD. (Ex.1010, ’758 patent, 15:50-16:6; *see also id.*, 3:5-29; Ex.1002, Albini, ¶ 111).

6. Dix (Ex.1033).

Dix published in 2006, and thus constitutes prior art under 35 U.S.C. § 102. The Examiner did not consider Dix. (*See* Ex.1001, ’069 patent, References Cited). Dix teaches pharmaceutical formulations comprising agents capable of inhibiting VEGF; the VEGF-Trap fusion protein (aflibercept) disclosed in Holash (Ex.1004) is Dix’s “preferred” VEGF antagonist. (*See* Ex.1033, Dix, Abstract; *id.*, [0005], [0014], [0030]).

The VEGF-Trap sequence disclosed in Dix is the same sequence for aflibercept required under the Challenged Claims. (*Compare* Ex.1001, '069 patent, SEQ ID NO:1 & SEQ ID NO:2, *with* Ex.1033, Dix, 9-11 (SEQ ID NO:3 & SEQ ID NO:4); Ex.1002, Albini, ¶ 113; Ex.1082; Ex.1083).

7. Mitchell (Ex.1030).

Mitchell first published online May 20, 2009, and thus constitutes prior art under 35 U.S.C. § 102.[15] To Petitioner's knowledge, Mitchell was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, '069 patent, References Cited). Mitchell discloses ranibizumab (LUCENTIS®) dosing trials, including MARINA and ANCHOR, which assessed the approved once-monthly regimen. (Ex.1030, Mitchell, 4-6). In addition, Mitchell expressly discusses the viability of less-frequent dosing, wherein monthly monitoring is coupled with flexible retreatment—in other words, PRN dosing. (*Id.*, 2; Ex.1002, Albini, ¶¶ 103-04).

[15] A publication is routinely provided online prior to print; its public availability and dissemination online allowing access to interested artisans exercising reasonable diligence. *VidStream LLC v. Twitter, Inc.*, 981 F.3d 1060, 1065 (Fed. Cir. 2020); Grünenthal GmbH v. Antecip Bioventures II LLC, No. PGR2019-00026, 2020 WL 4341822, at *8 (P.T.A.B. July 28, 2020); Ex.1003, Gerritsen, ¶¶ 39-40.

Mitchell further suggests the importance of loading doses, noting that "[i]nitiation regimens of fewer than three injections have not been assessed." (Ex.1030, Mitchell, 2, 4 ("[I]nitiation with three consecutive monthly injections appears optimal... Improvements occurred rapidly, and the largest VA gain occurred after the first injection.... Most VA improvement was seen during the initial 3-month phase with subsequent injections appearing to maintain the achieved benefit.")). Nonetheless, Mitchell concludes that "[p]rospective clinical trials would be valuable for investigating fewer injections in the initiation phase." (*Id.*, 4-5 (Fig.1(e)); Ex.1002, Albini, ¶¶ 103-06).

After MARINA and ANCHOR, researchers investigated less-frequent dosing schedules of ranibizumab. For example, Mitchell discloses the PrONTO and SUSTAIN studies, designed to deliver three initial monthly doses, followed by monthly monitoring coupled with dosing as-needed to maintain the VA gains observed during the first three months. (Ex.1030, Mitchell, 7-9; Ex.1002, Albini, 107). Mitchell reports that PrONTO and SUSTAIN delivered similar outcomes to MARINA and ANCHOR. (Ex.1030, Mitchell, 9-11; Ex.1002, Albini, 107). Mitchell thus concludes that appropriate dosing regimens may include a flexible, as- needed approach. (Ex.1030, Mitchell, 10-11; Ex.1002, Albini, ¶ 107).

Mitchell also incorporates Fung (Ex.1034) by reference. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("Incorporation

by reference provides a method for integrating material from various documents into a host document—a patent or printed publication in an anticipation determination.").

8. Lalwani (Ex.1035).

Lalwani published in 2009 and is prior art under 35 U.S.C. § 102. To Petitioner's knowledge, Lalwani was neither submitted nor cited during prosecution, and never considered by the Examiner. (Ex.1001, '069 patent, References Cited).

Lalwani discloses the two-year data from PrONTO. (*See* Ex.1035, Lalwani, 43). Lalwani echoes the prevailing sentiment at the time, calling into question whether monthly dosing is ideal, and discloses the PrONTO OCT-guided regimens which "could result in fewer injections and similar clinical outcomes" as compared to monthly dosing. (*Id.*, 44).

Lalwani reports a mean of 9.9 injections over two years resulting in mean improvements of 11.1 letters VA and 212 μm decreased retinal thickness, (*id.*, 43, 47-49), and concludes that the PrONTO PRN regimen was able to achieve outcomes comparable to the MARINA/ANCHOR monthly dosing regimens, (*id.*; Ex.1002, Albini, ¶¶ 108-09).

XII. GROUNDS FOR UNPATENTABILITY—DETAILED ANALYSIS.

A. ANTICIPATION AND OBVIOUSNESS.

1. Legal standards.

Anticipation requires that a "single prior art reference disclose[], either expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout*

Litig., 301 F.3d 1343, 1349 (Fed. Cir. 2002).

An inherent disclosure requires that "the natural result flowing from the operation as taught would result in the performance of the questioned function." *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010). Newly discovered results or new benefits of a known process directed to the same purpose are not patentable because such results are inherent. *Id.*; *see also In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007); *Perricone*, 432 F.3d 1378 (preamble reciting "method for treating skin sunburn" was inherently anticipated where the court found that "[i]f [the prior art reference] discloses the very same methods, then the particular benefits must naturally flow from those methods even if not recognized as benefits at the time of [the prior art's] disclosure").

In addition, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers*, 246 F.3d 1379. Here, the Challenged Claims require only a dosing regimen without any particular efficacy or result (Ex.1002, Albini, ¶ 42), and therefore, "proof of efficacy is not required in order for a [prior art] reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

Each anticipatory reference asserted herein (Heier-2009, Dixon, and Regeneron (30-April-2009), discussed below) is presumed enabling and it is

Regeneron's burden to rebut those presumptions. *See, e.g.*, *In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012); *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 659-60 (D. Del. 2014). Any attempted rebuttal here would be futile because each reference sets forth a clear method and dosing regimen that a skilled artisan would have no trouble following. Moreover, the Challenged Claims' preamble—even if it is assumed limiting (it is not)—does not help Regeneron. The asserted references each disclose Phase 2 data of a PRN regimen "treating" AMD. (*See, e.g.*, Ex.1020, Heier-2009, 45 ("mean improvements in BCVA of 9.0 letters . . . mean decreases in retinal thickness"); Ex.1006, Dixon, 1576 ("mean improvements of 9.0 . . . ETDRS letters" with 29% gaining ≥ 15 ETDRS letters at 52 weeks and "mean decreases in retinal thickness versus baseline of 143 μm ($p<0.0001$) in the 2.0 mg group . . . at 52 weeks as measured by OCT"). Thus, "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers*, 246 F.3d 1377. This inherency is illustrated by the very results Regeneron relied upon during prosecution, in addition to the results obtained in the Phase 2 CLEAR-IT-2 trial (published in, e.g., Dixon). Regeneron pointed to the Phase 3 results for VEGF Trap-Eye, which reported that "intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab." (Ex.1018, Heier-2012, 2537). From these results the authors concluded that "aflibercept is an

effective treatment for AMD, with the every-2- month regimen offering the potential to reduce the risk from monthly intravitreal injections." (*Id*.) Furthermore, the ranibizumab trials had already shown that an anti-VEGF biologic known to be successful with AMD was also successful at treating CRVO. (Ex.1036, Campochiaro, 794 ("results . . . suggest that intraocular injections of ranibizumab have a substantial effect on macular edema due to CRVO or BRVO")).

Obviousness. A patent claim is invalid under 35 U.S.C. § 103(a) if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *KSR*, 550 U.S. at 406. Furthermore, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* at 421.

The obviousness inquiry is "expansive and flexible," and the motivation to combine teachings found in separate prior art references can come from many sources, including: "[the] interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art." *Id.*

at 415; *see also id.* at 418.

When relying on secondary considerations—including long-felt need, failure of others, unexpected results, commercial success, copying, licensing, and industry praise—as evidence of non-obviousness, a patentee must establish a nexus between the secondary considerations and the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). There is no nexus unless the offered secondary consideration actually results from something that is both claimed and novel in the claim. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068-70, 1072 (Fed. Cir. 2011).

2. Grounds 1&2: Claims 1 and 9-12 are anticipated by both Heier-2009 and Dixon, respectively.

Heier-2009 and Dixon each disclose Regeneron's "CLEAR-IT-2" Phase 2 trial studying VEGF Trap-Eye as a therapy for treating AMD with four loading doses followed by a PRN dosing phase—thereby disclosing and thus anticipating all limitations of at least Challenged Claims 1 and 9-12.

Independent Claim 1. As set forth in the following table and confirmed by Dr. Albini (Ex.1002, Albini, ¶¶ 115-26), each of Heier-2009 and Dixon disclose every element of independent claim 1:

Claim 1	**Heier-2009:**	**Dixon:**
1. A method for treating an angiogenic eye disorder in a patient	"The CLEAR-IT 2 trial was a phase 2 study of the safety and efficacy of VEGF Trap-Eye . . . in patients with [AMD]." (Ex.1020, Heier-2009, 44). "At 1 year . . . there was a significant improvement in BCVA from baseline …" (*Id.*, 45). "Patients who received three monthly doses of 2.0 mg followed by as-needed dosing achieved mean improvements in BCVA of 9.0 letters from baseline." (*Id.*). (Ex.1002, Albini, ¶¶ 116, 120).	"VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of [AMD]." (Ex.1006, Dixon, 1573; *id.*, 1575). "Phase I data demonstrated acceptable safety and tolerability of VEGF Trap-Eye in the treatment of neovascular AMD." (*Id.*, 1577). Phase 2 patients "treated with 2.0 mg or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p<0.0001$) and 5.4 ($p<0.085$) ETDRS letters." (*Id*., 1576). "[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." (*Id.,* 1577). (Ex.1002, Albini, ¶¶ 116, 120).

Claim 1	**Heier-2009:**	**Dixon:**
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	"Patients with neovascular AMD were randomly assigned to receive monthly intravitreal injections of VEGF Trap-Eye 0.5 mg or 2.0 mg . . . for an initial 3-month fixed-dose period, after which they received the same doses on [a PRN] basis at monthly visits out to 1 year." (Ex.1020, Heier-2009, 45). (Ex.1002, Albini, ¶¶ 121-23).	"Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12) . . . . Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis." (Ex.1006, Dixon, 1576).[16] (Ex.1002, Albini, ¶¶ 121-123).
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(Ex.1020, Heier-2009, 45). (Ex.1002, Albini, ¶¶121-23).	(Ex.1006, Dixon, 1576). (Ex.1002, Albini, ¶¶ 121-23).

[16] In other words, patients received an "initial dose" (day 0), followed by sequential "secondary doses" at months 1, 2, and 3, followed by "tertiary" PRN doses thereafter. (Ex.1002, Albini, ¶ 121).

Claim 1	**Heier-2009:**	**Dixon:**
wherein each tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional;	(Ex.1020, Heier-2009, 45). (Ex.1002, Albini, ¶¶ 121-23).	"Following this fixed dosing period, patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. basis. Criteria for re-dosing included an increase in central retinal thickness . . . a loss of ≥ 5 ETDRS letters in conjunction with recurrent fluid by OCT, persistent fluid as indicated by OCT, new onset classic neovascularization, new or persistent leak on FA or new macular subretinal hemorrhage." (Ex.1006, Dixon, 1576).
wherein the VEGF antagonist is a receptor- based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids	"VEGF Trap-Eye is a purified formulation of VEGF Trap, a vascular endothelial growth factor (VEGF) receptor fusion protein that binds all forms of VEGF-A." (Ex.1020, Heier-2009, 44-45 (Fig.1)).[17]	VEGF Trap-Eye is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG." (*Id.*, 1576 (Fig.1)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same

[17] (Ex.1002, Albini, ¶ 125; *see* also Ex.1010, '758 patent, Fig.24A-C (setting forth the amino acid sequence and domain structure of VEGF Trap-Eye/aflibercept); Ex.1033, Dix, SEQ ID NO:4; Ex.1082).

Claim 1	**Heier-2009:**	**Dixon:**
130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.	(Ex.1002, Albini, ¶ 125).	molecular structure." (*Id.*, 1575). (Ex.1002, Albini, ¶ 125).

Claims 9 and 10. Claims 9 and 10 further limit the method of claim 1 to, *inter alia*, the angiogenic eye disorder, AMD. Heier-2009 discloses CLEAR-IT-2 data confirming the trial's PRN regimen was successful at treating AMD. (*Id.*, 44). Dixon similarly discloses the PRN regimen and results of CLEAR-IT-2 (Phase 2) to treat AMD. (Ex.1006, Dixon, 1573, 1576, 1579 (Ref. No. 45 ("VEGF Trap-Eye in Wet AMD. CLEAR-IT-2: Summary of One-Year Key Results")); Ex.1002, Albini, ¶¶ 127-31). Accordingly, Heier-2009 and Dixon disclose the additional limitation(s) of claims 9 and 10, and thus anticipate.

Claim 11. Claim 11 depends from claim 1 and further limits the claimed method to topical or intraocular administration. Intraocular administration refers to administration to the eye generally, while intravitreal administration, a subset of intraocular administration, refers to administration directly into the vitreous of the eye. (Ex.1002, Albini, ¶¶ 132-33; Ex.1001, '069 patent, 2:39-41). Heier-2009 and Dixon disclose monthly intravitreal injections of VEGF Trap-Eye. (Ex.1020, Heier-2009, 44-45; Ex.1006, Dixon, 1575; Ex.1002, Albini, ¶¶ 134-35). Accordingly,

Heier-2009 and Dixon disclose the additional limitation of claim 11, and thus anticipate.

Claim 12. Claim 12 depends from claim 1 and specifies the VEGF Trap-Eye/aflibercept nucleotide sequence. Both the amino acid and nucleotide sequences were disclosed in the prior art and well known to skilled artisans. (Ex.1002, Albini, ¶¶ 136-37; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence); *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)"); Ex.1033, Dix, SEQ ID NO:3; Ex.1083). The studies reported in Heier-2009 and Dixon are directed to VEGF Trap-Eye, and thus, each discloses the exact "VEGF antagonist" required by claim 12. Accordingly, Heier-2009 and Dixon anticipate.

3. Ground 3: Regeneron (30-April-2009) anticipates claims 1 and 9-12.

Regeneron (30-April-2009) describes the Phase 3 trials of VEGF Trap-Eye in CRVO using the claimed dosing regimens—thereby disclosing and thus anticipating all of the limitations of claims 1 and 9-12. According to Regeneron (30-April-2009), patients in the Phase 3 GALILEO and COPERNICUS trials received six monthly intravitreal injections, followed by PRN dosing for another six months. (Ex.1028, Regeneron (30-April-2009), 1).

Independent Claim 1. As set forth in the following table and further confirmed by Dr. Albini (Ex.1002, Albini, ¶¶ 138-44), Regeneron (30-April-2009)

discloses each and every element of independent claim 1:

Claim 1	**Regeneron (30-April-2009):**
1. A method for treating an angiogenic eye disorder in a patient	"[A] Phase 3 program evaluating the efficacy and safety of VEGF Trap-Eye in the treatment of CRVO ....." (Ex.1028, Regeneron (30-April-2009), 1). "[A]nti-VEGF treatment may help decrease vascular permeability and edema and prevent the growth of abnormal new blood vessels in the retina in patients with CRVO." (*Id.*).
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	"Patients in both studies will receive 6 monthly intravitreal injections….At the end of the initial 6 months, all patients will be dosed on a PRN (as needed) basis for another 6 months." (*Id.*).[18]
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(*Id.*).
wherein each tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as	(*Id.*).

[18] In other words, an "initial dose" (day 0) and five monthly "secondary doses," followed by "tertiary" PRN dosing. (Ex.1002, Albini, ¶¶ 139-42).

Claim 1	Regeneron (30-April-2009):
assessed by a physician or other qualified medical professional;	
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.	"VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PIGF). Investigational VEGF Trap-Eye is a specific blocker of VEGF-A and PIGF that has been demonstrated in preclinical models to bind these growth factors with greater affinity than their natural receptors." (*Id.*).[19]

Claims 9 and 10. Claim 9 limits the angiogenic eye disorders of claim 1 to, *inter alia*, AMD, DME, and CRVO, while claim 10 further limits to only AMD. Regeneron (30-April-2009) discloses, *inter alia*, Phase 3 trials directed to CRVO patients, and thus anticipates claim 9. (Ex.1028, Regeneron (30-April-2009), 1; Ex.1002, Albini, ¶¶ 145-49). Regeneron (30-April-2009) also discloses VEGF Trap-Eye clinical trials for AMD and thus anticipates claim 10.

Claim 11. Claim 11 depends from claim 1 and further limits the claimed method to topical or intraocular administration. Regeneron (30-April-2009) expressly discloses the intravitreal injection used in Phase 3 CRVO studies, and thus

[19] *See* supra note 11.

anticipates claim 11. (Ex.1028, Regeneron (30-April-2009), 1; Ex.1002, Albini, ¶¶ 150-53).

Claim 12. Claim 12 depends from claim 1 and specifies the VEGF Trap-Eye/aflibercept nucleotide sequence. As explained above, the amino acid and nucleotide sequences for aflibercept were disclosed in the prior art and well known to skilled artisans. (Ex.1002, Albini, ¶¶ 154-55; Ex.1010, '758 patent, Fig.24A-C; *id.*, 10:15-17; Ex.1033, Dix, SEQ ID NO:3; Ex.1083). The studies reported in Regeneron (30-April-2009) are directed to VEGF Trap-Eye, and thus, Regeneron (30-April-2009) discloses the exact "VEGF antagonist" required by claim 12. Accordingly, Regeneron (30-April-2009) anticipates.

4. Ground 4: VIEW1/VIEW2 disclosures in Dixon anticipate and/or render obvious claims 1 and 8-12.

During prosecution, Regeneron told the Examiner that the VIEW1/VIEW2 every-eight-week dosing regimen represented a "PRN treatment protocol" within the scope of the Challenged Claims:

> [VIEW1/VIEW2] results clearly show that by administering the VEGF antagonist ***in accordance with a dosage regimen as claimed in independent claim 1***, it is possible to treat angiogenic eye disorders such as AMD while administering doses on a less frequent basis.

(Ex.1017, '069 FH, 1/30/2017 Amendment, 6 (emphasis added); *id.*, 7). Based upon that representation, Regeneron expressly relied on purported "unexpected results" from VIEW1/VIEW2 (as published in Heier-2012) to secure the Challenged Claims. (*Id.*, 6-8).[20] Applying that same interpretation of the claims here, Dixon's disclosure of Regeneron's Phase 3 VIEW1/VIEW2 trials in AMD patients anticipate, or at least render obvious, Challenged Claims 1 and 8-12.

a. Anticipation.

Independent Claim 1. Dixon discloses the exact VIEW1/VIEW2 dosing regimens that Regeneron told the Examiner represented a "PRN treatment protocol" "as claimed" in independent claim 1. Applying Regeneron's interpretation of the Challenged Claims, Dixon discloses each and every element of Challenged Claim 1 for the additional reasons set forth in the following table:

[20] *See* supra § VIII(B).

Claim 1	**Dixon:**
1. A method for treating an angiogenic eye disorder in a patient	"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.1006, Dixon, 1573). "Two Phase III studies in wet AMD, VIEW 1 and VIEW 2, are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye." (*Id.*, 1577; *id.*, 1577-79 (describing DME and RVO studies)).
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	Phase 3 study "will evaluate the safety and efficacy of..... 2.0 mg at an 8 week dosing interval (***following three monthly doses***)"—i.e., doses at week 0, 4, 8, 16, 24, 32, 40, and 48. (*Id.*, 1576 (emphasis added)).
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(*Id.*).
wherein each tertiary dose is administered on an as-needed/pro re nata (PRN) basis, based on visual and/or anatomical outcomes as assessed by a physician or other qualified medical professional;	(*Id.*; Ex.1017, '069 FH, 1/30/2017 Amendment, 6-7 (telling Examiner VIEW1/VIEW2 represents a "PRN treatment protocol," "as claimed in independent claim 1"); *id*., 6 (VIEW1/VIEW2 trial regimens are "of the type claimed")).
wherein the VEGF antagonist is a receptor-based chimeric molecule	VEGF Trap-Eye is "a fusion protein of binding domains of VEGF receptors-1

Claim 1	Dixon:
comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.	and -2 attached to the Fc fragment of human IgG." (Ex.1006, Dixon, 1576 (Fig.1)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575). (Ex.1002, Albini, ¶ 166).

The amino acid sequence and structural information for VEGF Trap-Eye recited in the last "wherein" clause was well known and widely-published to skilled artisans. (Ex.1010, '758 patent, Fig.24A-C; *id.*, 10:15-17; Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1033, Dix, SEQ ID NO:4; Ex.1082; Ex.1002, Albini, ¶ 166). Dixon's express disclosure of VEGF Trap-Eye thus anticipates. *In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991) ("extrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference").

Claim 8. Claim 8 depends from claim 1 and further limits the claimed regimen to "only two secondary doses" "wherein each secondary dose is administered 4 weeks after the immediately preceding dose"—i.e., doses at weeks 0 (initial dose), 4, and 8 (two secondary doses). Applying Regeneron's interpretation that the Challenged Claims encompass the VIEW1/VIEW2 dosing regimen (and thus can be supported by so-called "unexpected results" from that study), Dixonexpressly discloses the claim 8 limitation. (Ex.1006, Dixon, 1576 ("three

monthly doses," i.e., an initial dose at day 0 and two secondary doses at weeks 4 and 8); Ex.1002, Albini, ¶¶ 175-78). Accordingly, Dixon anticipates.

Claims 9 and 10. Claims 9 and 10 further limit the method of claim 1 to, *inter alia*, the angiogenic eye disorder, AMD. Dixon expressly discloses AMD treatment regimens. (Ex.1006, Dixon, 1573 ("Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD"); *id.*, 1576 (the Phase 3 trial "will enroll ~1200 patients with neovascular AMD"; Ex.1002, Albini, ¶¶ 179-82). Accordingly, Dixon discloses the additional limitation(s) of claims 9 and 10, and thus, anticipates.

Claim 11. Claim 11 depends from claim 1 and further limits the claimed method to topical or intraocular administration. The Phase 3 studies disclosed in Dixon expressly "evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (Ex.1006, Dixon, 1576). Intravitreal injection is a type of intraocular administration that refers to administration directly into the vitreous of the eye. (Ex.1002, Albini, ¶¶ 183-86; Ex.1001, '069 patent, 2:39-41). Accordingly, Dixon discloses the additional limitation of claim 11 and thus, anticipates.

Claim 12. Claim 12 depends from claim 1 and specifies the VEGF Trap-Eye/aflibercept nucleotide sequence. Both the amino acid and nucleotide sequences were disclosed in the prior art and well known to skilled artisans. (Ex.1010, '758 patent, Fig.24A-C; *id.*, 10:15-17; *see also* Ex.1002, Albini, ¶¶ 187-89; Ex.1033, Dix,

SEQ ID NO:3; Ex.1083). The Dixon studies are directed to VEGF Trap-Eye and thus Dixon discloses the exact "VEGF antagonist" required by claim 12. Accordingly, Dixon anticipates.

b. Obviousness.

Challenged Claims 1 and 8-12 are also invalid as obvious over Dixon.

Motivation to Combine. Dixon, alone, unequivocally provides the motivation to combine the skilled artisan's knowledge and prior art teachings to achieve the method(s) of, at least, Challenged Claims 1 and 8-12. (Ex.1006, Dixon, 1577 ("significant time and financial burden falls on patients during their [monthly] treatment course" and "[d]esirable attributes for emerging therapies for neovascular AMD include . . . decreased dosing intervals"); Ex.1002, Albini, ¶ 168). Furthermore, as evidenced by the prior art, skilled artisans had been practicing the claimed regimens—and obvious variations thereof—for years before January 2011. For example, skilled artisans routinely began therapy with three monthly loading doses and followed with PRN re-treatment as determined during scheduled monthly visits—otherwise known as "PrONTO-style dosing." (Ex.1025, Engelbert-2010, 1369 ("PrONTO-style dosing has become popular . . . .")). Indeed, by 2009, such PrONTO-style regimens were widely used for intravitreal anti-angiogenesis agents

like ranibizumab and bevacizumab.[21] And, standard re-treatment was routinely done in accordance with predetermined criteria, such as an increase in retinal thickness or OCT-detected fluid and/or losses in visual acuity. (Ex.1002, Albini, ¶ 169). In addition, Dixon's disclosure of the positive results of the Phase 2 AMD (CLEAR-IT-2) study showed that VEGF Trap-Eye could be administered on a PRN-basis following four initial loading doses (which is only one more loading dose than the three loading doses in claim 8).

Finally, and in addition to the aforementioned invalidating disclosures, the VIEW1/VIEW2 trials incorporated a second year, wherein PRN dosing was expressly used. Accordingly, a skilled artisan would have been further motivated given that the Dixon-disclosed studies merely adopted the already popular, PrONTO-style regimens for treating vitreoretinal disease. (Ex.1002, Albini, ¶ 170).

As a result, the claimed regimen consisting of an initial dose, followed by one or more monthly loading doses and PRN dosing thereafter, was obvious to skilled artisans. This is particularly true in view of the prior art, VIEW1/VIEW2 regimens, which (i) were based on known, pre-existing treatment regimens, and (ii) Regeneron admitted fall within the scope of the Challenged Claims.

[21] Though not FDA-approved for intravitreal use, bevacizumab was widely used off-label by ophthalmologists. (Ex.1037, Steinbrook, 1409-12).

Reasonable Expectation of Success. Skilled artisans would have also reasonably expected success using the VIEW1/VIEW2 regimen based on the same, aforementioned prior art disclosures. For example, Regeneron's Phase 2 trials had already generated positive results and Dixon further discloses Regeneron's launch of Phase 3 trials involving >2000 patients based on those positive results—in other words, skilled artisans expected success. (Ex.1006, Dixon, 1576 (reporting increases in visual acuity and mean decreases in retinal thickness resulting from the Phase 2 regimen); Ex.1002, Albini, ¶¶ 171-73).

In sum, Dixon also renders Challenged Claims 1 and 8-12 obvious based on the same disclosures applied in the anticipation analysis above, in light of Regeneron's reliance on VIEW1/VIEW2 data to secure allowance; the publicly disclosed motivation to reduce injection frequency; and the reasonable expectation of success provided by at least the positive Phase 2 data.

5. Ground 5: The Challenged Claims are obvious over Heier-2009 in combination with either Mitchell or Dixon—and, optionally, either the '758 patent or Dix.

The Heier-2009 (Phase 2 AMD) disclosures are discussed in detail above (*see supra* § XII.A.2), and that discussion is incorporated by reference herein. As set forth in more detail below, a skilled artisan prior to 2011 (i) would have been motivated to combine the teachings in Heier-2009 with prior art teachings related to other methods of treating intravitreal eye disorders with anti-VEGF less-frequent dosing

regimens—the most notable (and main competitor in that market) at the time being ranibizumab (LUCENTIS®), as disclosed in, e.g., Mitchell[22]; and (ii) based on the combination of prior art including Heier-2009 would have reasonably expected success applying the LUCENTIS dosing regimen disclosed in Mitchell (i.e., three monthly loading doses followed by PRN) to VEGF Trap-Eye. In addition, a skilled artisan would have been motivated to combine the teachings in Dixon regarding Regeneron's VIEW trials for VEGF Trap-Eye—which also evaluated a dosing regimen comprising three monthly loading doses—with Heier-2009 to achieve a less-frequent, PRN dosing regimen with a reasonable expectation of success.[23]

---

[22] As explained in § XI(B)(7) above, Mitchell expressly incorporates by reference Fung, which discloses the PrONTO twelve-month results. In addition, as set forth in § XI(B)(8) above, Lalwani discloses the two-year PrONTO data (including the dosing regimen) and further confirms the PrONTO, PRN dosing regimen was able to achieve outcomes comparable to the MARINA/ANCHOR monthly dosing regimens. (Ex.1035, Lalwani, 43, 47-49). Accordingly, Heier-2009 may also be combined with Lalwani to equally render the Challenged Claims invalid as obvious.

[23] As explained in detail above (supra § XII(A)(2)), both Heier-2009 and Dixon are directed toward and expressly disclose VEGF Trap-Eye, for which the molecular structure was widely published and well known to skilled artisans. As such, the

a. A skilled artisan would have been motivated to combine Heier-2009 with either Mitchell or Dixon.

Prior to January 2011, a skilled artisan would have been motivated to combine the Heier-2009 disclosures of success treating AMD with a monthly loading/PRN dosing regimen, with either one of (i) Mitchell, which disclosed anti-VEGF (ranibizumab) regimens comprising three loading doses (weeks 0, 4, and 8) followed by PRN dosing; or (ii) Dixon, which disclosed the VIEW1/VIEW2 that comprised three monthly loading doses (weeks 0, 4, and 8). It was therefore obvious to combine these teachings to arrive at the Challenged Claims. *See KSR*, 550 U.S. at 418.

b. Independent Claim 1.

Heier-2009. As explained in detail above (*supra* § XI(B)(3)), Heier-2009 describes Regeneron's CLEAR-IT-2 trial, wherein patients received, *inter alia*, monthly intravitreal injections through three months (i.e., doses at weeks 0, 4, 8, and

---

amino acid and nucleic acid sequences are inherent features of the VEGF Trap-Eye disclosed in both Heier-2009 and Dixon. Notwithstanding, the aforementioned combinations (Heier-2009 plus either Mitchell or Dixon) may be further combined with either the '758 patent or Dix, which expressly disclose the VEGF Trap-Eye sequences otherwise known to skilled artisans. (*See* supra n.11; § XI(B)(5)-(6); Ex.1010, '758 patent, Fig.24A-C; Ex.1033, Dix, SEQ ID NO:3 & SEQ ID NO:4; Ex.1082; Ex.1083)).

12), followed by PRN dosing for the first year. (Ex.1020, Heier-2009, 44-45). Moreover, Heier-2009 reports significant improvements in BCVA and decreases in retinal thickness, compared to baseline. (*Id.*). Given that success, a skilled artisan would have recognized the therapeutic potential of VEGF Trap-Eye, and would have been motivated to explore less-frequent dosing regimens given the well-documented concerns over monthly dosing. (Ex.1006, Dixon, 1256-57; Ex.1002, Albini, ¶¶ 190-92).

Mitchell. The skilled artisan would have naturally turned to literature regarding VEGF Trap-Eye's main competitor in anti-VEGF treatment: ranibizumab (LUCENTIS®). (Ex.1002, Albini, ¶ 193). Mitchell discloses ranibizumab clinical studies, including PrONTO and SUSTAIN, which were designed to assess less frequent dosing. (*Id.*). PrONTO specifically involved "three consecutive monthly injections," (i.e., weeks 0, 4, and 8) followed by PRN dosing. (Ex.1030, Mitchell, 6; Ex.1034, Fung, 569-70; Ex.1002, Albini, ¶¶ 194-96). SUSTAIN also involved ranibizumab administered in three monthly injections (i.e., weeks 0, 4, and 8), followed by PRN dosing based on visual acuity and retinal thickness criteria. (Ex.1030, Mitchell, 7; Ex.1002, Albini, ¶ 195). The gains from the three-month phase were largely maintained which suggested that "flexible, guided dosing with fewer ranibizumab injections and monthly monitoring can maintain efficacy outcomes." (Ex.1030, Mitchell, 7; Ex.1002, Albini, ¶¶ 195-96).

Further, a skilled artisan would not have been dissuaded from Mitchell just because ranibizumab and VEGF Trap-Eye are different molecules. (Ex.1030, Mitchell, 9 (Table 3)). Despite the differences in molecular structure, clinical trials revealed similar efficacy. (*Compare* Ex.1034, Fung, 566, 577 (PrONTO regimen resulting in a mean change in visual acuity of 9.3 letters after one year), *with* Ex.1006, Dixon, 1576 (CLEAR-IT-2 patients receiving a 2.0 mg monthly loading dose regimen followed by PRN saw mean improvements of 9.0 letters after one year); Ex.1018, Heier-2012, 2537 (reporting all aflibercept groups, including monthly dosing, "were noninferior and clinically equivalent to monthly ranibizumab for the primary end point."); Ex.1002, Albini, ¶ 198).

Dixon. Dixon discloses CLEAR-IT-2, wherein patients receiving VEGF Trap-Eye monthly loading doses followed by PRN experienced significant improvements. (Ex.1006, Dixon, 1576). Upon that success, and given concerns over frequent intravitreal injections, a skilled artisan also would have been motivated to drop the loading doses from the four used in CLEAR-IT-2 (Phase 2) to the three used in VIEW (Phase 3), also disclosed in Dixon. (*Id.*; Ex.1002, Albini, ¶¶ 191-92).

In sum, Heier-2009 discloses the use of VEGF Trap-Eye in treating AMD, an angiogenic eye disorder and a successful PRN dosing phase. Both Mitchell and Dixon teach anti-VEGF regimens for AMD employing an initial dose (week 0), one or more secondary doses administered four weeks after the immediately preceding

dose (weeks 4 and 8)—for a total of three loading doses, and tertiary PRN dosing. A skilled artisan naturally would have been motivated to combine the successful PRN regimen of CLEAR-IT-2 from Heier-2009 with the widely used loading regimen of three monthly doses disclosed in Mitchell and Dixon—to arrive at a regimen falling squarely within Challenged Claim 1. The "assessed by a physician" limitation is a pure mental step not entitled to any patentable weight. *See, e.g., King Pharms.*, 616 F.3d at 1278 (an otherwise unpatentable method claim does not become patentable because it includes a step of "informing someone"). Notwithstanding, PRN dosing includes physician assessment (*see* Ex.1002, Albini, ¶ 119), and both Mitchell and Dixon expressly disclose the "assessed by a physician" limitation of Challenged Claim 1. (Ex.1030, Mitchell, 6-7 ("OCT-guided variable dosing"; "[r]etreatment criteria [include]..."; "additional treatment guided by the following criteria..."); Ex.1006, Dixon, 1576 ("Criteria for re-dosing included ...")).

Accordingly, Heier-2009 provides clear motivation to seek out and consult references setting forth extended anti-VEGF regimens, like those disclosed in Mitchell and Dixon. Given the positive Phase 2 results, a skilled artisan would have reasonably expected a PRN regimen with three monthly loading doses to succeed in treating an angiogenic eye disorder. Consequently, Challenged Claim 1 would have been obvious over Heier-2009 in combination with either Mitchell or Dixon.

c. Claim 8.

Claim 8 depends from claim 1 and further limits the claimed dosing regimen to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose"—i.e., doses at weeks 0 (initial dose), 4, and 8 (two secondary doses). This is the exact loading dose regimen used in the ranibizumab PrONTO and SUSTAIN trials disclosed in Mitchell, (Ex.1030, Mitchell, 6-7), as well as, the VEGF Trap-Eye VIEW Phase 3 trials disclosed in Dixon. (Ex.1006, Dixon, 1576; Ex.1002, Albini, ¶¶ 204-07). Accordingly, and for the reasons discussed above for claim 1, claim 8 would have been obvious.

d. Claims 9 and 10.

Claims 9 and 10 further limit the method of claim 1 to treating, *inter alia*, AMD (an angiogenic eye disorder). Heier-2009, Mitchell and Dixon all disclose methods of treating AMD. (Ex.1006, Dixon; Ex.1020, Heier-2009; Ex.1030, Mitchell; Ex.1002, Albini, ¶¶ 208-10). Accordingly, and for the reasons discussed above for claim 1, claims 9 and 10 would have been obvious.

e. Claim 11.

Claim 11 further limits the method of claim 1 to topical or intraocular administration. Intraocular administration refers to administration to the eye generally, while intravitreal administration, a subset of intraocular administration,

refers to administration directly into the vitreous of the eye and is expressly disclosed in the prior art. (Ex.1006, Dixon; Ex.1020, Heier-2009; Ex.1030, Mitchell; Ex.1002, Albini, ¶¶ 211-13; Ex.1001, '069 patent, 2:39-41). Accordingly, and for the reasons discussed above for claim 1, claim 11 would have been obvious.

f. Claim 12.

Claim 12 depends from claim 1 and specifies the VEGF Trap-Eye nucleotide sequence. Both the amino acid and nucleotide sequences were disclosed in the prior art and the molecule was well known to skilled artisans. (Ex.1010, '758 patent, Fig.24A-C; *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)"); Ex.1002, Albini, ¶¶ 214-16; Ex.1033, Dix, SEQ ID NO:3; Ex.1083).

Therefore, through their disclosure of VEGF Trap-Eye, Heier-2009, and Dixon disclose the "VEGF antagonist" required by claim 12. Accordingly, and for the reasons discussed above for claim 1, claim 12 would have been obvious.

g. A skilled artisan would have reasonably expected success.

Heier-2009 plus Mitchell. A skilled artisan would have reasonably expected success using the Heier-2009 PRN regimen alone, or combining it with the PrONTO loading dose regimen for ranibizumab (as disclosed in Mitchell) given the successful reports using PRN regimens for VEGF Trap-Eye, as well as for ranibizumab. (Ex.1020, Heier-2009, 45; Ex.1030, Mitchell, 9 (Table 3); Ex.1002, Albini, ¶¶ 191, 194). Further, a skilled artisan would have had a reasonable expectation of success

given the similar efficacy observed between the two biologics. Specifically, the ranibizumab AMD PrONTO regimen of three monthly loading doses followed by PRN dosing resulted in a mean change in visual acuity of 9.3 letters after one year. (Ex.1030, Mitchell, 9; Ex.1034, Fung, 566, 577; Ex.1035, Lalwani, 47). Similarly, in CLEAR-IT-2, patients receiving a monthly loading dose regimen followed by PRN dosing saw mean improvements of 9.0 letters after one year. (Ex.1006, Dixon, 1576). This observed similarity in efficacy between ranibizumab and VEGF Trap-Eye also is consistent with later reports on the results of the VIEW trials, in which "[a]ll aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point." (Ex.1018, Heier-2012, 2537; Ex.1002, Albini, ¶¶ 197-98).

Heier-2009 plus Dixon. A skilled artisan would have reasonably expected success combining the PRN regimen of Heier-2009 with the loading dose regimen disclosed in Dixon, which amounts to essentially reducing the four loading doses from CLEAR-IT-2 to the three used in VIEW1/VIEW2. As described in detail above, Dixon discloses both CLEAR-IT-2 and VIEW dosing regimens, which incorporated three and two "secondary doses," respectively. Dixon further discloses the significant improvements observed after monthly loading doses in CLEAR-IT-2, providing skilled artisans a reasonable expectation that the VIEW loading doses would be successful. (Ex.1006, Dixon, 1576; Ex.1002, Albini, ¶¶199-201).

* * *

For the reasons stated above, claims 1 and 8-12 are obvious in view of Heier-2009 alone or in combination with either Mitchell or Dixon.

6. No Secondary Considerations.

Petitioner is not aware of any secondary considerations that would support a finding of non-obviousness. Further, even if such secondary considerations exist, they are (i) not relevant or applicable to the robust anticipation grounds presented herein, and (ii) cannot overcome the strong *prima facie* cases of obviousness discussed above. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1245-47 (Fed. Cir. 2010).

As an initial matter, the Challenged Claims do not require any particular levels of efficacy. Thus, for example, Regeneron's allegation—asserted during prosecution, (Ex.1017, '069 FH, 1/30/2017 Amendment, 6-9)—that the less frequent regimen of Challenged Claims produced "unexpected results" is entirely irrelevant. *Ormco*, 463 F.3d at 1311-12; *Kao*, 639 F.3d at 1068-69. However, assuming Regeneron asserts those same statements to argue unexpected results here, the arguments were inaccurate and omitted highly pertinent information.

First, Regeneron argued that the claimed PRN dosing regimen was exemplified by the VIEW1/VIEW2 regimen. Regeneron then argued that the VIEW1/VIEW2 regimens, as disclosed in post-art Heier-2012, yielded unexpected

results—while failing to disclose that the VIEW1/VIEW2 regimen had been the subject of numerous *prior art* disclosures (e.g., Dixon, Adis) ***dating back to at least 2008***. (Ex.1002, Albini, ¶¶ 218-19).

Second, Regeneron characterized the standard of care at the time as monthly dosing, and sought to distinguish the claims from that "standard of care," ignoring that PRN dosing could result in monthly injections. In other words, monthly dosing falls within the scope of the issued claims of the '069 patent.

Third, Regeneron's characterization of monthly dosing as the standard of care ignored treating physicians' actual practice at the time, which often utilized regimens with three monthly doses followed by PRN treatment. (Ex.1002, Albini, ¶ 220). Regeneron's statements are also belied by Regeneron's own published clinical studies reporting regimens with less frequent dosing, as well as Genentech's approach in the ranibizumab clinical trials. (*See, e.g.*, SUSTAIN (PRN dosing after three monthly loading doses); EXCITE (quarterly dosing after three monthly loading doses); PrONTO (PRN dosing after three monthly loading doses); SAILOR (PRN dosing after three monthly loading doses); and PIER (quarterly dosing after three monthly loading doses); Ex.1030, Mitchell, 9-10 (providing a summary of each of the above studies); Ex.1031, Massin, 55 (RESOLVE study); Ex.1002, Albini, ¶ 221).

Fourth, there is nothing surprising or unexpected about the every-eight-week results in light of the promising Phase 2 PRN dosing regimen results obtained by

Regeneron—results that were omitted from their arguments to the Patent Office. Phase 2 data showed a mean gain in visual acuity of nine letters and a mean decrease in retinal thickness of 143 μm. (Ex.1002, Albini, ¶ 222). This led Regeneron to announce in a press release (also withheld from the Patent Office), that "an 8-week dosing schedule may be feasible." (Ex.1012, Regeneron (28-April-2008), 1; Ex.1002, Albini, ¶ 222).

Fifth, Regeneron's claims that there were "an infinite number of different treatment protocols" (Ex.1017, '069 FH, 1/30/2017 Amendment, 6) to choose from, ignored the practical realities facing physicians who were administering intravitreal anti-VEGF agents at the time. As Dr. Albini explains, ophthalmologists were concerned about the frequency of injections under a straight monthly regimen. (Ex.1002, Albini, ¶ 223). Thus, when considering possible VEGF Trap-Eye regimens, monthly dosing would have been avoided if possible, and anything more frequent than monthly would not have been considered. Given the prevalence of PRN and treat-and-extend approaches already being used by ophthalmologists, it is neither surprising nor unexpected that a new entrant to the anti-VEGF market would have considered a PRN dosing regimen (which Regeneron has argued would include the bimonthly regimen used in VIEW1/VIEW2). Lastly, the choice of three initial monthly loading doses was also not surprising given the prevalence of that exact loading regimen in the anti-VEGF studies being conducted at the time. (*See, e.g.*,

Ex.1030, Mitchell, 9-10 (disclosing SUSTAIN; EXCITE; PrONTO; SAILOR; and PIER); Ex.1002, Albini, ¶ 223).

Sixth, to the extent Regeneron argues long-felt but unmet need, it will be unable to establish a "need" or show that any such need was "long-felt." By 2010, the claimed PRN dosing regimen was not only publicly disclosed in Regeneron's CLEAR-IT-2 study and the extensive ranibizumab art, it also was already in use among ophthalmologists administering anti-VEGF agents. (Ex.1002, Albini, ¶ 225). Consequently, any "unmet" need had already been fulfilled well before the '069 patent was filed. (*Id.*).

Should Regeneron argue that any purported commercial success of EYLEA® is pertinent to patentability, Regeneron will be unable to establish that such purported commercial success is attributable to the claimed regimen. (*Id.*, ¶ 226).

Petitioner reserves the right to more specifically respond to any assertions of secondary considerations that Regeneron alleges during this proceeding.

XIII. CONCLUSION.

The Challenged Claims are unpatentable in view of the prior art. Petitioner therefore requests that trial be instituted and the Challenged Claims cancelled.

Respectfully Submitted,

Dated: December 9, 2021

/Teresa Stanek Rea/

Teresa Stanek Rea
Reg. No. 30,427
Deborah H. Yellin
Reg. No. 45,904
Shannon M. Lentz
Reg. No. 65,382
CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300

Counsel for Petitioner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing Petitioner Apotex Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 9,669,069 B2, and Exhibits 1001-1083, and Apotex's Motion for Joinder were served on December 9, 2021, via FedEx Priority Overnight on the Patent Owner at the correspondence address of record for U.S. Patent No. 9,669,069 B2 as evidenced in Public Pair:

Regeneron – Bozicevic Field & Francis LLP
201 Redwood Shores Parkway
Suite 200
Redwood City, CA 94065

Courtesy copies of the foregoing were also served via email on the counsel of record for the Petitioner and Patent Owner in *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc*, IPR2021-00880 as follows:

Mylan Pharmaceuticals, Inc.	**Regeneron Pharmaceuticals, Inc.**
MYL_REG_IPR@rmmslegal.com	regeneroneyleaiprs@arnoldporter.com

/Shannon Lentz/
Shannon Lentz (Reg. No. 65,382)

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,933 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a).

Dated: December 9, 2021

/Shannon Lentz/
Shannon Lentz (Reg. No. 65,382)