UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC., CELLTRION, INC.,
and APOTEX, INC.,
Petitioners

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner

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Case IPR2021-00880[1]
Patent No. 9,669,069 B2

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PATENT OWNER RESPONSE

[1] IPR2022-00257 and IPR2022-00301 have been joined with this proceeding.

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2001	Exhibit Number Unused
2002	Exhibit Number Unused
2003	Lucentis (ranibzumab injection) label, revised June 2010
2004	Ex. (a)(1)(a) to Tender Offer Statement to Momenta, filed with SEC on September 2, 2020
2005	Press Release, Johnson & Johnson, *Johnson & Johnson to Acquire Momenta Pharmaceuticals, Inc., Expanding Janssen's Leadership in Novel Treatments for Autoimmune Diseases*, dated August 19, 2020
2006	Press Release, Johnson & Johnson, *Johnson & Johnson Completes Acquisition of Momenta Pharmaceuticals, Inc*, dated October 1, 2020
2007	Press Release, THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 2008)
2008	Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)" versions available and updated on 17 March 2008.
2009	U.S. Patent App. No. 2006/0058234
2010	Excerpts from J.M. Berg *et al*., Biochemistry (5th Ed. 2002)
2011	M.W. Stewart & P.J. Rosenfeld, *Predicted Biological Activity of Intravitreal VEGF Trap*, Br. J. Opthamol 92:667-68 (2008)
2012	P. Iacono *et al*., *Antivascular Endothelial Growth Factor in Diabetic Retinopathy*, Dev. Opthamol. 46:39-53 (2010)
2013	D.V. Do *et al*., *An Exploratory Study of the Safety, Tolerability and Bioactivity of a Single Intravitreal Injection of Vascular Endothelial Growth Factor Trap-Eye in Patients With Diabetic Macular Oedema*, Br. J. Opthamol 93:144-49 (2009)
2014	J.W. Moroney *et al.*, *Aflibercept in Epithelial Ovarian Carcinoma*, Future Oncol 5(5):591-600 (2009)
2015	U.S. Patent Publication 2010/0160233 A1 to Bissery *et al*., published June 24, 2010
2016	T. Hachiya et al., *Increase in respiratory cost at high growth temperature is attributed to high protein turnover cost in Petunia x hybrida petals*, Plant, Cell, and Environment, 30:1269-1283 (2007)

2017	M. Piques et al., *Ribosome and transcript copy numbers, polysome occupancy and enzyme dynamics in Arabidoposis*, Molecular Systems Biology 5: Article number 314 (2009)
2018	Jaffe et al., *Differential Response to Anti-VEGF Regimens in Age-Related Macular Degeneration Patients with Early Persistent Retinal Fluid*, Ophthalmology 2016;123:1856-1864 (2016)
2019	Eylea (aflibercept) Injection label, revised May 2016
2020	A Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (SPECTRI), NCT02247531, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT02247531?term=lampalizumab&phase=2&draw=2&rank=2
2021	A Study Investigating the Efficacy and Safety of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (CHROMA), NCT02247479, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT02247479?term=lampalizumab&phase=2&draw=2&rank=3
2022	Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD(PANDA-2), NCT03630952, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT03630952?term=NCT03630952&draw=2&rank=1
2023	Efficacy and Safety Trial of Conbercept Intravitreal Injection for Neovascular AMD(PANDA-1), NCT03577899, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT03577899?term=NCT03577899&draw=2&rank=1
2024	A Phase 3 Safety and Efficacy Study of Fovista® (E10030) Intravitreous Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy, NCT01944839, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT01944839?term=fovista&phase=2&draw=2&rank=1

2025	A Phase 3 Safety and Efficacy Study of Fovista® (E10030) Intravitreous Administration in Combination With Lucentis® Compared to Lucentis® Monotherapy, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT01940900?term=fovista&phase=2&draw=2&rank=2
2026	S. Elvidge, *Opthotech's Fovista crashes out in wet AMD*, BIOPHARMADIVE (Aug. 14, 2017), *available at*, https://www.biopharmadive.com/news/opthotech-fovista-phase-3-failure-setback-novartis/449248/
2027	X. Li et al., *Safety and Efficacy of Conbercept in Neovascular Age-Related Macular Degeneration: Results from a 12-Month Randomized Phase 2 Study: AURORA Study*, Ophthalmology 2014:121:1740-1747 (2014)
2028	Regeneron Pharmaceuticals Inc., "VEGF Trap-Eye CLEAR-IT 2 Final Primary Endpoint Results" presented at the 2007 Retina Society Conference in Boston, Massachusetts (September 30, 2007)
2029	Bhisitkul, Robert B. and Stewart, Jay M., *Alternative anti-VEGF treatment regimens in exudative age-related macular degeneration*, Expert Rev. Ophthalmol., Vol. 5, No. 6 (2010).
2030	Park, Young Gun et al., *New Approach to Anti-VEGF Agents for Age-Related Macular Degeneration*, Journal of Ophthalmology (2012).
2031	Spaide, Richard, *Ranibizumab According to Need: A Treatment for Age-related Macular Degeneration*, American Journal of Ophthalmology (April 2007)
2032	Boyer, David S., *A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration*, Ophthalmology, Vol. 116, No. 9 (Sept. 2009)
2033	Lucentis (ranibzumab injection) label, revised March 2018
2034	U.S. Patent No. 7,303,746
2035	U.S. Patent No. 7,521,049
2036	U.S. Patent No. 7,303,747
2037	U.S. Patent No. 7,306,799
2038	Macugen (pegaptanib sodium injection) label submitted with NDA 21-756
2039	Press Release, *Regeneron, Regeneron Reports Fourth Quarter and Full Year 2012 Financial and Operating Results*, dated February 14, 2013
2040	Press Release, *Regeneron, Regeneron Reports Fourth Quarter and Full Year 2019 Financial and Operating Results*, dated February 6, 2030

2041	Press Release, Regeneron, *Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)*, dated December 20, 2010
2042	J.P. Levine *et al.*, *Macular Hemorrhage in Neovascular Age-related Macular Degeneration After Stabilization With Antiangiogenic Therapy*, Retina 29(8):1074-79 (2009)
2043	Press Release, *Thomson Reuters Links Discovery and Literature Citation Databases*, dated January 4, 2010
2044	Declaration of Victoria Reines
2045	Declaration of Daniel Reisner
2046	Declaration of Matthew M. Wilk
2047	Declaration of Jeremy Cobb
2048	Expert Declaration of Dr. Lucian V. Del Priore, M.D., Ph.D. - CONFIDENTIAL MATERIAL - SUBJECT TO PROTECTIVE ORDER
2049	Expert Declaration of Dr. Alexander M. Klibanov, Ph.D. - CONFIDENTIAL MATERIAL - SUBJECT TO PROTECTIVE ORDER
2050	Expert Declaration of David M. Brown, M.D.
2051	Exhibit Number Unused
2052	Exhibit Number Unused
2053	A Study of Aflibercept Administered in Combination With Pemetrexed and Cisplatin in Patients With Advanced Carcinoma, NCT00794417, ClinicalTrials.gov (Posted Nov. 20, 2008), https://clinicaltrials.gov/ct2/history/NCT00794417?A=1&B=1
2054	A Study of Intravenous Aflibercept With Docetaxel in Chinese Patients With Solid Tumors, NCT01148615, ClinicalTrials.gov (Posted Jun. 22, 2010), https://clinicaltrials.gov/ct2/history/NCT01148615?A=1&B=1
2055	Ferrara et al., *Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration.* 26 RETINA 859 (2006)
2056	Kim et al., *A Brief History of Anti-VEGF for the Treatment of Ocular Angiogenesis*, 181 THE AMERICAN JOURNAL OF PATHOLOGY 376 (2012)
2057	Ramazi et al., *Post-translational modifications in proteins: resources, tools and prediction methods*, 2021 DATABASE 1 (2021)

2058	Bork et al., *Increasing the Sialylation of Therapeutic Glycoproteins: The Potential of the Sialic Acid Biosynthetic Pathway*, 98 J. PHARM. SCI. 3499 (2009)
2059	Regeneron Sample Analysis Report: PK06005-9-SA-01V1 (2006) ("Koehler-Stec Report") - CONFIDENTIAL MATERIAL - SUBJECT TO PROTECTIVE ORDER
2060	Regeneron Pharmaceuticals Protocol VGFT-OD-0605, Table 14.2.3/2a - Summary of Proportion of Vision Loss from Baseline to Week 96, Last Observations Carried Forward (Full Analysis Set) ("VGFT-OD-0605 Analysis Summary") - CONFIDENTIAL MATERIAL - SUBJECT TO PROTECTIVE ORDER
2061	Kim et al., *Eyes that Do Not Meet the Eligibility Criteria of Clinical Trials on Age-Related Macular Degeneration: Proportions of the Real-World Patient Population and Reasons for Exclusion*, 2021 JOURNAL OF OPHTHALMOLOGY1 (2021)
2062	Nieto et al., *Ocular silicon distribution and clearance following intravitreal injection of porous silicon microparticles*, 116 EXP EYE RES. 161 (2013)
2063	Fernández-Ferreiro et al., *Preclinical PET Study of Intravitreal Injections*, 58 INVEST OPHTHALMOL. VIS SCI. 2843 (2017)
2064	Shen et al., *Clearance of Intravitreal Voriconazole*, 48 INVEST. OPHTHALMOLOGY & VISUAL SCI. 2240 (2007)
2065	Cabo et al., *The Clearance of Intravitreal Gentamicin*, 92 AMERICAN J. OPHTHALMOLOGY 59 (1981)
2066	Pflugfelder et al., *Intravitreal Vancomycin: Retinal Toxicity, Clearance, and Interaction with Gentamicin*, 105 ARCH. OPHTHALMOL. 831 (1987)
2067	Hirokawa et al., *Tau Proteins: The Molecular Structure and Mode of Binding on Microtubules*, 107 J. CELL BIOL. 1449 (1988)
2068	Prangé et al., *Exploring Hydrophobic Sites in Proteins with Xenon or Krypton*, 30 PROTEINS: STRUCTURE, FUNCTION, AND GENETICS 61 (1998)
2069	Kleiger et al., *The 1.7 Å Crystal Structure of BOI: A Study of How Two Dissimilar Amino Acid Sequences Can Adopt the Same Fold*, 299 J. MOL. BIOL. 1019 (2000)
2070	Demarest et al., *Optimization of the Antibody C_H3 Domain by Residue Frequency Analysis of IgG Sequences*, 335 J. MOL. BIOL. 41 (2004)
2071	Kuhlmann et al., *Lessons Learned from Biosimilar Epoetins and Insulins*, 10 BRITISH J. DIABETES VASC. DISEASE 90 (2010)

2072	Murphy et al., *Protein Folding, Misfolding, Stability and Aggregation: An Overview,* in MISBEHAVING PROTEINS - PROTEIN (MIS)FOLDING, AGGREGATION, AND STABILITY; Murphy et al., Eds., Springer, New York, 2006
2073	Zaltrap non-comparability issue: Regeneron Sanofi Analytical Investigation Workshop (March 14, 2014) - CONFIDENTIAL MATERIAL - SUBJECT TO PROTECTIVE ORDER
2074	Solá et al., *Effects of Glycosylation on the Stability of Protein Pharmaceuticals*, 98 J. PHARM. SCI. 1223 (2009)
2075	Eylea® Approval Letter (November 18, 2011)
2076	Cantu et al., *Thioesterases: A New Perspective Based on Their Primary and Tertiary Structures*, 19 PROTEIN SCIENCE 1281 (2010)
2077	Chen et al., *Carboxylic ester hydrolases: Classification and database derived from their primary, secondary, and tertiary structures*, 25 PROTEIN SCIENCE 1942 (2016)
2078	Aflibercept in Combination With Docetaxel in Metastatic Androgen Independent Prostate Cancer (VENICE), NCT00519285, ClinicalTrials.gov (Posted Aug. 22, 2007), https://clinicaltrials.gov/ct2/history/NCT00519285?V_1
2079	Aflibercept and Standard Chemotherapy (R-CHOP) in First Line of Non Hodgkin B-Cell Lymphoma, NCT00644124, ClinicalTrials.gov (Posted Mar. 26, 2008), https://clinicaltrials.gov/ct2/history/NCT00644124?A=1&B=1
2080	Heier, *VEGF Trap-Eye for Exudative AMD*, RETINAL PHYSICIAN, Apr. 2009 ("Heier Retinal Physician 2009")
2081	Curriculum Vitae of Dr. Dr. Lucian V. Del Priore, M.D., Ph.D.
2082	Curriculum Vitae of Dr. Alexander M. Klibanov, Ph.D.
2083	Curriculum Vitae of Dr. David Mark Brown, M.D.
2084	Anthony P. Adamis, *Ocular Angiogenesis: Vascular Endothelial Growth Factor and Other Factors*, *in* Retinal Pharmacotherapy 23 (Quan Dong Nguyen et al. eds., 2010)
2085	David M. Brown et al., *Ranibizumab Versus Verteporfin Photodymanic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study*, 116 Ophthalmology 57 (2009)
2086	Carl D. Regillo, David M. Brown et al., *Randomized, Double-masked, Sham-controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1*, 145 Am. J. Ophthalmology 239 (2008)

2087	Prema Abraham et al., *Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2*, 150 Am. J. Ophthalmology 315 (2010)
2088	Irene Barbazetto et al., *Dosing Regimen and the Frequency of Macular Hemorrhages in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab*, 30 Retina 1376 (2010)
2089	Daniele Cruz, *PIER Data Suggest a Need for Tailored Injection Schedule*, Ocular Surgery News, (Sept. 1, 2006), https://www.healio.com/news/ophthalmology/20120331/pier-data-suggest-a-need-for-tailored-injection-schedule
2090	*Retinal Physician Symposium Covers Broad Range of Topics*, Retinal Physician (Sept. 1, 2006), https://www.retinalphysician.com/issues/2006/september-2006/retinal-physician-symposium-covers-broad-range-of
2091	CDER Approved Labeling for BLA Application 125156 (Lucentis®) (2006)
2092	Ursula Schmidt-Erfurth et al., *Efficacy and Safety of Monthly Versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCITE Study*, 118 Ophthalmology 831 (2011)
2093	Ron Margolis & K. Bailey Freund, *Hemorrhagic Recurrence of Neovascular Age-Related Macular Degeneration Not Predicted by Spectral Domain Optical Coherence Tomography*, 4 Retinal Cases & Brief Rep. 1 (2010)
2094	David M. Brown et al., *Primary Endpoint Results of a Phase II Study of Vascular Endothelial Growth Factor Trap-Eye in Wet Age-related Macular Degeneration*, 118 Ophthalmology 1089 (2011)
2095	Jeff Heier, David M. Brown et al., *The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing*, 118 Ophthalmology 1099 (2011)
2096	Clinical Study Agreement Between Vitreoretinal Consultants and Regeneron Pharmaceuticals, Inc. (July 31, 2007) - CONFIDENTIAL MATERIAL - SUBJECT TO PROTECTIVE ORDER
2097	FDA, Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry (Nov. 2016)
2098	CDER, Statistical Review for Application Number 125387 (Nov. 18, 2011)

2099	FDA, 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results (Jan. 2017)
2100	Jeffrey S. Heier & FOCUS Study Group, *Abstract: Intravitreal Ranibizumab (Lucentis™) with Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Year One Results*, Am. Soc'y Retina Specialists Ann. Meeting 94 (2005)
2101	*Safety and Efficacy of Repeated Intravitreal Administration of Vascular Endothelial Growth Factor (VEGF) Trap in Patients With Wet Age-Related Macular Degeneration (AMD)*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT00320788.
2102	Wells, John A., et al. (2015), "Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema," The New England Journal of Medicine 372(13): 1193–1203
2103	*Ongoing Treatment for Patients with Neovascular AMD*, Retinal Physician (Oct. 1, 2007), https://www.retinalphysician.com/issues/2007/october-2007/ongoing-treatment-for-patients-with-neovascular-am
2104	Andrew E. Mathis, *Fine-Tuning Your Anti-VEGF Injection Protocols: The Second Article in Our Series Recapping Research and Analysis Presented at Our Annual Meeting*, Retinal Physician (Oct. 1, 2009), https://www.retinalphysician.com/issues/2009/october-2009/fine-tuning-your-anti-vegf-injection-protocols
2105	Scott W. Cousins, *Controversies in the Long-term Management of Neovascular AMD: The Role of Imaging in Clinical Decision Making*, Retinal Physician (Jan. 1, 2010), https://www.retinalphysician.com/issues/2010/jan-feb/controversies-in-the-long-term-management-of-neova
2106	Jerry Helzner, *Lucentis After 1 Year: Doctors Praise This Practice-transforming Therapy—But Find Drawbacks*, Retinal Physician (July 1, 2007), https://www.retinalphysician.com/issues/2007/july-aug/lucentis-after-1-year
2107	Press Release, *Regeneron Announces FDA Approval of Eylea® (Aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration* (Nov. 18, 2011), available at https://www.fiercebiotech.com/biotech/regeneron-announces-fda-approval-of-eylea™-aflibercept-injection-for-treatment-of-wet-age
2108	FDA, Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014), https://www.fda.gov/media/86377/download

2109	*Macugen for Proliferative Diabetic Retinopathy Study With Extended Dosing (M-PDRS ED)*, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT01486771
2110	Ron P. Gallemore & David Nguyen, *When Anti-VEGF Treatment Fails: Retina Specialists Are Charting New Territory and Learning How to Spot and React to Failed Anti-VEGF Therapy*, Rev. Ophthalmology (Mar. 20, 2008)
2111	Press Release, Kanghong Pharmaceutical, *Announcement of Chengdu Kanghong Pharmaceutical Group Co., Ltd. on Stopping the Global Multi-center Clinical Trial of Conbercept Ophthalmic Injection*, http://epaper.zqrb.cn/html/2021-04/10/content_716426.htm?div=-1 (original)
2112	Press Release, Kanghong Pharmaceutical, *Announcement of Chengdu Kanghong Pharmaceutical Group Co., Ltd. on Stopping the Global Multi-center Clinical Trial of Conbercept Ophthalmic Injection*, http://epaper.zqrb.cn/html/2021-04/10/content_716426.htm?div=-1 (English translation)
2113	Michael Thomas et al., *Comparative Effectiveness of Aflibercept for the Treatment of Patients with Neovascular Age-related Macular Degeneration*, 7 Clinical Ophthalmology 495 (2013)
2114	Matthew Ohr & Peter K. Kaiser, *Aflibercept in Wet Age-related Macular Degeneration: A Perspective Review*, 3 Therapeutic Advances Chronic Disease 153 (2012)
2115	*FDA Approves Eylea for Wet Age-Related Macular Degeneration*, Drugs.com, (Nov. 18, 2011), https://www.drugs.com/newdrugs/fda-approves-eylea-wet-age-related-macular-degeneration-2955.html
2116	Press Release, *Regeneron Announces FDA Approval of Eylea® (Aflibercept) Injection for the Treatment of Wet Age-Related Macular Degeneration* (Nov. 18, 2011)
2117	Macugen Approval Letter (December 17, 2004)
2118	Brown DM, et al., *Ranibizumab versus verteporfin for neovascular age-related macular degeneration*, N Engl J Med. 2006;355(14):1432-44
2119	Rosenfeld PJ, Brown DM, et al., *Ranibizumab for neovascular age-related macular degeneration*, N Engl J Med. 2006;355(14):1419-31

2120	Press Release, *Genentech, Inc. Submits Biologics License Application For FDA Review Of Lucentis(TM) In Wet Age-Related Macular Degeneration* (Dec. 30, 2005), available at https://www.biospace.com/article/releases/genentech-inc-submitsbiologics-license-application-for-fda-review-of-lucentis-tm-in-wetage- related-macular-degeneration-/
2121	Genentech News Release, *FDA Approves Lucentis for the Treatment of Wet Age-Related Macular Degeneration*, (June 30, 2006)
2122	A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE), NCT00473330, ClinicalTrials.gov (December 22, 2021), https://www.clinicaltrials.gov/ct2/show/NCT00473330
2123	A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE), NCT00473382 ClinicalTrials.gov (December 22, 2021), https://clinicaltrials.gov/ct2/show/NCT00473382
2124	A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion (BRAVO), NCT00486018 (December 22, 2021), https://clinicaltrials.gov/ct2/show/NCT00486018
2125	A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion (CRUISE), NCT00485836 (December 22, 2021), https://clinicaltrials.gov/ct2/show/NCT00485836
2126	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO), NCT00943072 (December 22, 2021), https://clinicaltrials.gov/ct2/show/NCT00943072
2127	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO) (GALILEO), NCT01012973 (December 22, 2021), https://clinicaltrials.gov/ct2/show/NCT01012973
2128	VGFT-OD-0605 (VIEW 1 Trial) Protocol Signature Page-CONFIDENTIAL MATERIAL - SUBJECT TO PROTECTIVE ORDER
2129	Transcript of Deposition of Mary Gerritsen, Ph.D. (January 14, 2022)
2130	Transcript of Deposition of Thomas Albini, M.D. (January 20, 2022)

Patent Owner Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron") respectfully submits that Petitioner Mylan Pharmaceuticals Inc. ("Petitioner" or "Mylan") has not carried its burden of demonstrating by a preponderance of the evidence that Claims 1 and 8-12 ("the Challenged Claims") of U.S. Patent No. 9,669,069 ("the '069 Patent," Ex.1001) are unpatentable.

I. INTRODUCTION

Petitioner, who is developing a biosimilar of EYLEA® for the treatment of angiogenic eye disorders, filed this challenge to try to invalidate Regeneron's '069 Patent, which covers an alternate approved dosing regimen for EYLEA.

Before the development of EYLEA, ranibizumab (Lucentis®) or off-label bevacizumab (Avastin®) were the standard-of-care for treatment of angiogenic eye disorders. While both ranibizumab and bevacizumab provided highly effective treatment, the great burden of monthly eye injections and office visits led to extensive efforts in the art to decrease injection frequency and physician monitoring. Ex.1018, 2537, 2545. However, fixed quarterly or "as needed" (*pro re nata*) dosing regimens without monthly monitoring visits were not effective at maintaining vision. Ex.1018, 2537; Ex.1001, 1:55-59.

Regeneron sought to develop a therapy that would finally improve ***and*** maintain visual acuity with extended time between injections. The '069 Patent discloses and claims the administration of a sequence-limited VEGF antagonist using a dosing regimen that includes a single initial dose of the VEGF antagonist,

followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, where the tertiary doses are "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."

Petitioner's anticipation challenges fail because its cited references do not expressly or inherently disclose the recited amino acid or nucleic acid sequences of the Challenged Claims. Because the art contained only an inconsistent and incomplete description of "VEGF Trap-Eye," the recited sequence information is not inherent in Petitioner's Grounds and cannot demonstrate anticipation of the Challenged Claims.

Petitioner's Ground 4 anticipation challenge fails for the additional reason that Dixon does not disclose the dosing regimen recited in Claim 8.

Finally, Petitioner's Ground 5 obviousness challenges fail both because the person of ordinary skill in the art (the "POSA") would not have had a reason to modify Regeneron's Phase 2 dosing regimen by omitting a monthly loading dose; to the contrary, the results from Regeneron's Phase 2 trial, as well as the art taken as a whole, would have discouraged the POSA from doing so. Moreover, the POSA would not have been motivated to modify a fixed 8-week tertiary dosing regimen to become a PRN tertiary dosing regimen, as required by each of the Challenged Claims.

Thus, Patent Owner respectfully requests that the Board affirm the validity of the Challenged Claims of the ’069 Patent.

II. THE STATE OF THE ART

Angiogenic eye disorders, such as neovascular age-related macular degeneration (“wet AMD” or “wAMD”), diabetic macular edema (“DME”) and macular edema following retinal vein occlusion (“RVO”), are characterized by abnormal growth or permeability of blood vessels in the retina and elevated ocular levels of VEGF. Ex.2050 (Brown Decl.), ¶¶26-28. Early treatments for wAMD, such as laser ablation and photodynamic therapy (“PDT”), only slowed eventual vision loss. *Id*., ¶27. By the early 2000’s, scientists and clinicians began to investigate anti-VEGF agents to treat angiogenic eye disorders. Macugen® was the first anti-VEGF agent approved for treatment of angiogenic eye disorders, specifically wAMD, but like laser and PDT treatments, it only slowed the rate of vision loss. *Id*., ¶30.

Clinical testing of Genentech’s drug, ranibizumab (Lucentis®), established the potential therapeutic benefit of anti-VEGF therapy. The Lucentis clinical trials showed for the first time that patients with wAMD could experience ***vision gains*** (7-9 letters on average) as opposed to merely slowing vision loss. Ex.2050, ¶31-39; Ex.2130 (Albini Tr.), 28:18-29:3. Shortly after its approval in June 2006, Lucentis

(or off-label Avastin)[2] became the prevailing standard-of-care for treatment of angiogenic eye disorders. Ex.2050, ¶40-42; Ex.2130 (Albini Tr.), 153:2-6 (Lucentis and off-label Avastin as standard of care by 2011).

No longer was merely slowing disease progression considered to be effective treatment for angiogenic eye disorders and, consequently, use of Macugen all but disappeared. Ex.2050, ¶42; Ex.2130 (Albini Tr.), 155:10-17, 156:11-157:11; 193:19-194:15. As Mylan's expert, Dr. Albini, aptly put it, by 2011, Macugen was "ancient history." Ex.2130 (Albini Tr.), 28:18-29:3. Instead, the standard-of-care for wAMD quickly moved to frequent intravitreal injections of Lucentis (or off-label Avastin), which could improve patients' vision and often maintain those gains over the course of treatment. Ex.2050, ¶¶40-42; Ex.2130 (Albini Tr.), 153:2-6 (Lucentis and off-label Avastin as standard of care by 2011).

Nonetheless, the risk of rare but serious adverse events from intravitreal injection, together with the significant burden of monthly office visits, led to extensive efforts in the art to decrease injection and monitoring frequency. Ex.2050, ¶¶45, 151-155; Ex.1018, 2537. Numerous attempts were made to decrease injection

[2] Avastin (bevacizumab), an anti-VEGF antibody, was approved by FDA for the treatment of metastatic colorectal cancer in February 2004. Ex. 2156. However, by late 2005, ophthalmologists had reported successfully using Avastin off-label for the treatment of wAMD. Ex.2050, ¶¶29, 40.

or monitoring frequency with ranibizumab, including the PIER, PrONTO, SAILOR, EXCITE, and SUSTAIN clinical trials. Ex.2050, ¶¶46-69, 160-164. Unfortunately, these efforts at extended dosing in the art failed because they were not effective at maintaining vision. Ex.1018, 2537.

PIER, EXCITE, and SAILOR[3] tested fixed quarterly dosing of ranibizumab. Each study reported that initial visual acuity gains from monthly loading doses were lost over the quarterly maintenance period. Ex.2130 (Albini Tr.), 234:5-6, 234:12-19, 237:1-7; Ex.2050, ¶¶47-62, 68. Not surprisingly, fixed quarterly dosing of ranibizumab was never adopted in clinical practice. Ex.1018, 2537; Ex.2130 (Albini Tr.), 33:12-34:12; 237:8-15; Ex.2050, ¶68. PrONTO, a 40 patient, non-randomized study, ***required 24 dilated office visits in the first year*** and, even so, subjects experienced vision-threatening complications. Ex.2050, ¶¶63-67; Ex.2130 (Albini Tr.), 254:11-19. SUSTAIN, which tested PRN maintenance dosing, reported loss of visual acuity gains in the PRN maintenance period. Ex.2050, ¶¶67-68. Ultimately, these efforts to develop extended dosing regimens resulted in inferior results (*i.e.*, loss of visual acuity, vision-threatening complications) as compared to monthly dosing with ranibizumab. *Id*., ¶¶68-69. Before the priority

[3] SAILOR tested three monthly loading doses followed by PRN with quarterly monitoring visits such that study subjects could not receive retreatment more frequently than once quarterly. Ex.2130 (Albini Tr.), 235:20-236:13.

filing date, despite enormous effort, no one had been able to extend the dosing interval while maintaining the high level of efficacy of the standard-of-care. Ex.2050, ¶69; Ex.1018, 2545.

III. THE '069 PATENT

The invention claimed by the '069 Patent is the administration of a sequence-limited VEGF antagonist using a dosing regimen that includes a single initial dose of the VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist, where the tertiary doses are "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.1001, Claim 1.

The '069 Patent contains one independent claim and 11 dependent claims. Petitioner challenges claims 1 and 8-12 in this proceeding.

Claim 1 recites:

> 1. A method for treating an angiogenic eye disorder in a patient, 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;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

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;

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.

Claim 8 depends from Claim 1 and further specifies that "only two secondary doses are administered to the patient" and that each secondary dose is administered 4 weeks after the immediately preceding dose. In other words, Claim 8 recites three monthly loading doses before administering the tertiary dose(s). Claims 9-11 depend from Claim 1 and further specify the angiogenic eye disorder being treated, as well as the mode of delivery. Claim 12 specifies that the VEGF antagonist fusion protein is encoded by the nucleic acid sequence of SEQ ID NO: 1.

IV. CLAIM CONSTRUCTION[4]

Regeneron respectfully submits that "assessed by a physician or other

[4] Regeneron disagrees with Petitioner's definition of the POSA. Pet. 22. The POSA, for purposes of the '069 Patent, is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists.

qualified medical professional" is a positive limitation of the claim that should be afforded patentable weight.

Petitioner also proposes a construction for "tertiary dose" and argues that the preamble "A method for treating an angiogenic eye disorder in a patient" is not a positive limitation of the claim. Paper 1, 13-23. While Regeneron disagrees with Petitioner's proposed constructions, Regeneron does not advance claim construction positions for these terms at this time because construction of these terms is not necessary to resolve the arguments presented in Mylan's Petition. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (explaining it is only necessary to "construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'").[5]

However, Regeneron does not believe that the parties' differing definitions of "the POSA" matter for any argument in this Patent Owner Response.

[5] However, if the Board decides to construe "method of treating" or "tertiary dose" in this IPR, it should do so consistently with the constructions Regeneron has proposed in its contemporaneously filed Response in IPR2021-00881 relating to the '338 Patent, since the '069 Patent was filed as a continuation from the '338 Patent. *See* IPR2021-00881, Paper 10, 31-37; *see Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1378 (Fed. Cir. 2019) ("Where multiple patents

Petitioner likewise proposes constructions for (1) "4 weeks" and "pro re nata (PRN)"; and (2) "VEGFR1 Component," "VEGFR2 Component" and the "Multimerization Component." Paper 1, 18-19. Again, Regeneron does not advance claim construction positions for these terms because the Board does not need to construe these terms to resolve the arguments presented in this POR. *Nidec*, 868 F.3d at 1017.

V. GROUNDS 1-4: PETITIONER FAILS TO DEMONSTRATE THAT "VEGF TRAP-EYE" WAS KNOWN TO CORRESPOND TO SEQ ID NO:1 OR SEQ ID NO:2

In its Institution Decision, the Board assumes that "by the time VEGF Trap-Eye was in clinical trials, it was almost certainly well known in the art what its chemical composition (including amino acid sequence) was, if only to avoid regulatory and clinical confusion." Paper 21, 37. But the record evidence does not support this assumption. To the contrary, it is undisputed that VEGF Trap-Eye was not publicly available before EYLEA's FDA approval on November 18, 2011. Ex.2130 (Albini Tr.), 319:16-320:9; Ex.2050, ¶¶70-72. Regeneron's clinical trials involving VEGF Trap-Eye were conducted under strict confidentiality, as was Regeneron's submission of information to FDA regarding VEGF Trap-Eye pre-

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

approval.[6] Thus, the amino acid or nucleic acid sequence of VEGF Trap-Eye was not available before the priority filing date of the '069 Patent unless the identity of those sequences was publicly disclosed.

Anticipation requires "each and every claim limitation [to be] found either expressly or inherently in a single prior art reference." *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1274 (Fed. Cir. 2010) (quotations omitted). Because none of Petitioner's references—Dixon (Grounds 1 and 4), Heier-2009 (Ground 2), and Regeneron (30-April-2009) (Ground 3)—discloses, either expressly or inherently, the amino acid or nucleic acid sequence of VEGF Trap-Eye, none of these references anticipates the Challenged Claims.

A. Petitioner's Grounds 1-4 References Do Not Expressly Disclose the Amino Acid or Nucleic Acid Sequence of VEGF Trap-Eye

Petitioner relies on disclosures in Heier-2009, Dixon and Regeneron (30-April-2009) to purportedly anticipate the claimed sequence information for "VEGF Trap-Eye." But these references do not disclose any sequence information for "VEGF Trap-Eye." *See* Ex.2129 (Gerritsen Tr.), 109:15-110:3 (agreeing that

[6] Regeneron required its clinical investigators to sign confidentiality agreements that restricted disclosure of information regarding VEGF Trap-Eye. Ex.2050, ¶¶70-72 (citing Ex.2096 and Ex.2128). Likewise, all information concerning VEGF Trap-Eye submitted to FDA was maintained as confidential pre-approval. *See* 21 CFR §§ 601.50, 601.51.

the amino acid sequence of VEGF Trap-Eye is not disclosed in Dixon); Ex.2130 (Albini Tr.), 341:13-16; *see also* Ex.2049 (Klibanov Decl.), Section IX; Ex.2048 (Del Priore Decl.), Section X; Ex.1020; Ex.1028. Consequently, Petitioner must show inherent anticipation of the amino acid and nucleic acid limitations of claims 1 and 14, respectively. For the reasons detailed below, Petitioner has failed to establish inherent anticipation because the POSA would not have necessarily known or determined that "VEGF Trap-Eye" had the claimed amino acid or nucleic acid sequence based on publicly available information as of the priority filing date of the '069 Patent.

B. Petitioner's Grounds 1-4 References Do Not Inherently Disclose the Amino Acid or Nucleic Acid Sequence of VEGF Trap-Eye

Because Petitioner's Grounds 1-4 references do not expressly disclose the amino acid or nucleic acid sequence of VEGF Trap-Eye, Petitioner asserts that the claimed sequences are inherently disclosed by those references. But "[i]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F3d 629, 639 (Fed. Cir. 2011) (citing *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). To succeed on inherency, Petitioner must establish that the amino acid or nucleic acid sequence of VEGF Trap-Eye "is necessarily present" in the Ground 1-4 references. *Continental Can Co. USA v. Monsanto*, 948 F.2d 1264, 1268 (Fed. Cir. 1991); *see also Rexnord Indus., LLC v. Kappos*, 705

F.3d 1347, 1355 (Fed. Cir. 2013) ("[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation."). *Rosco, Inc. v. Mirror Lite Co.*, misread by Petitioner (Paper 1, 27), further states that "the question is not whether" practice of the prior art reference "inherently results" in the claimed limitation, "but whether one skilled in the art would read the [prior art reference] as inherently disclosing the invention." 304 F.3d 1373, 1380-81 (Fed. Cir. 2002) (reversing a finding of inherent anticipation where there was no evidence that the POSA would understand a prior art reference as inherently disclosing the invention).

The Federal Circuit has also instructed that inherency cannot be invoked where there is an incomplete disclosure of a claimed composition in the prior art—*e.g.*, VEGF Trap-Eye—because "incomplete description of the [claimed] composition elements denied skilled artisans from having access to that composition." *See Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018) (clinical studies of a testosterone supplement ("TU") did not inherently disclose the composition because it was not reported and thus unknown to a skilled artisan years after the priority date). The Board's decision in *Amgen, Inc. v. Alexion Pharms.*, provides further guidance. In *Amgen*, the Board rejected an inherent anticipation argument based on the assertion that a prior art reference's disclosure of the name "eculizumab" inherently disclosed the claimed protein. IPR2019-00741, Paper 15, 20 (P.T.A.B. Aug. 30, 2019). Because the

Board found that the term "eculizumab" referred to at least two different proteins in the prior art, including the unclaimed "Thomas IgG4 isotype eculizumab," the prior art "would not have necessarily led the skilled artisan to the claimed antibody," there was no inherent anticipation. *Id*., 24-25.

As in *Endo* and *Amgen*, Petitioner's references do not adequately disclose the amino acid or nucleic acid sequence of VEGF Trap-Eye such that the POSA would have known that it necessarily corresponded to the claimed sequences. Petitioner's cited references do not identify the amino acid or nucleic acid sequences of "VEGF Trap-Eye," nor do they show that "VEGF Trap-Eye" must have had the recited sequences of the Challenged Claims. Consequently, Petitioner's references do not anticipate the Challenged Claims.

1. Dixon Does Not Disclose That VEGF Trap-Eye Shares the Same Amino Acid Sequence of Aflibercept

Petitioner relies heavily on Dixon's statement that "VEGF Trap-Eye" and aflibercept (the oncology product) share a "molecular structure" to show inherency of the VEGF Trap-Eye amino acid sequence. Ex.1006, 1575. Dixon, however, does not say that "VEGF Trap-Eye" and aflibercept have the same amino acid sequence and, further, a shared "molecular structure" does not necessarily mean an identical amino acid sequence. It is well-established that protein molecules, like VEGF Trap-Eye, have multiple levels of "structure," including primary, secondary, tertiary, and quaternary structures. Ex.2049, ¶¶50-56 (citing Ex.2010, 4); Ex.2048, ¶66-72. The term "molecular structure" was repeatedly used in the literature to

refer to the three-dimensional structure of the protein, rather than the protein's amino acid sequence. Ex.2049, ¶57-63 (citing Ex.2067, 1449) ("This study was designed to disclose the ***molecular structure*** of tau" proteins that have rodlike three-dimensional structure.) (emphasis added).

Importantly, the POSA would have known that proteins with different amino acid sequences may have the same molecular structure or *vice versa*. Ex.2049, ¶61-63 (citing Ex.2076 at 1292) (noting that thioesterases can have "very different primary structures but common tertiary structures"); *id.*, ¶58 (citing Ex.2069, 1019, 1026) (noting that over 1000 pairs of proteins with similar molecular structures but ***dissimilar*** amino acid sequences have been cataloged); *id*., ¶59 (citing Ex.2070, 41) (murine and bovine antibody domains have "***surprisingly similar structures*** and stabilities, ***considering the marginal sequence conservation*** between the two molecules."); *id*., ¶63 ("[A] protein with a given amino acid sequence expressed in *E. coli* may have a different overall structure when it is expressed in a mammalian host cell."); *see also* Ex.2048, ¶¶68-69.

Moreover, Dixon itself suggests that the "molecular structure" of VEGF Trap-Eye refers to a more general selection and arrangement of receptor binding domains and an Fc region, not a precise amino acid or nucleic acid sequence. Ex.2049, ¶¶65-66; Ex.2048, ¶¶71-72; Ex.2130 (Albini Tr.), 337:17-21 ("Dixon is describing the structure of VEGF Trap-Eye by its key binding domains in the Fc region [in Fig. 1]. A. That's correct."). Specifically, Dixon uses the term "molecular

structure" right after explaining that: "***Structurally***, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (Fig. 1)." Ex.1006, 1573, 1576 fig. 1. Figure 1 shows a stylized version of VEGF receptors 1 and 2 and the binding domains that lead to the creation of a VEGF Trap molecule Ex.1006, 1576.

Simply put, the POSA would understand that Dixon's statements concerning the "molecular structure" of VEGF Trap-Eye could have referred to the protein's three-dimensional (3D) structure, or overall configuration of VEGF binding domains, rather than its primary structure (*i.e.*, amino acid sequence). Ex.2049, ¶¶49-66; Ex.2048, ¶¶66-72. Petitioner's experts agree with this understanding. Ex.2129 (Gerritsen Tr., 73:25-74:4 ("[T]he protein's ***molecular structure*** will refer to its secondary structure, correct? A. … I think that it would refer to the structural information. That's what it says, "'structure.'") (emphasis added); Ex.2130 (Albini Tr.), 107:16-22 (agreeing that when he refers to structural changes in a protein he is "referring to changes in the 3D structure of the protein.").

2. The POSA Would Have Had Reason to Doubt That VEGF Trap-Eye Corresponded to Only Aflibercept

a. The POSA could have concluded that VEGF Trap-Eye was a genus of proteins with different amino acid sequences

The structural information that Dixon provides for VEGF Trap-Eye—"a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment"—was insufficient to distinguish VEGF Trap-Eye from

any other protein comprising a VEGFR1 domain 2, VEGFR2 domain 3, and a human Fc region. Rather, the POSA would have understood Dixon's description to correspond to a genus of protein sequences reported in the art, which understanding would have been confirmed by variability in the reported molecular weights of "VEGF Trap-Eye." Ex.2049, ¶67-83.

Regeneron developed, tested, and published on a variety of engineered VEGF fusion proteins that it called "VEGF Trap" molecules, only some of which included both the VEGFR1 and VEGFR2 binding domains. Ex.2049, ¶68-75 (citing Ex.1004, 11394). Even the term "VEGF TrapR1R2," which is a subset of VEGF Trap proteins, was known to encompass a genus of protein sequences, any one of which could satisfy Dixon's structural definition, but would not necessarily possess the amino acid sequence of the Challenged Claims. Ex.2049, ¶¶68-75 (identifying multiple VEGF TrapR1R2 proteins with different amino acid sequences). For example, the '758 Patent (Ex.1010) and Dix (Ex.1033) disclose the amino acid and nucleic acid sequences for a VEGF $Trap_{R1R2}$ protein that does ***not*** satisfy the sequence limitations of the Challenged Claims. Ex.2049, ¶¶69-74; Ex.1010, 10:4-6 (SEQ ID NO: 11 and SEQ ID NO:12 disclose the amino acid and nucleic acid sequences for Flt1D2.Flk1D3.FcΔC1(a)); Ex.1033 (SEQ ID NO:1 and SEQ ID NO:2). Indeed, each of the references on which Petitioner relies includes multiple VEGF-Trap sequences, including multiple VEGF-TrapR1R2 sequences.

b. The prior art reported VEGF Trap-Eye to have different molecular weights than aflibercept

In addition to the genus of published protein sequences falling within the description of "VEGF Trap-Eye," the POSA would have been aware of different reported molecular weights for "VEGF Trap-Eye." For example, the prior art reports that "VEGF Trap-Eye is a ***110-kDa*** recombinant protein," and that "VEGF Trap-Eye (Regeneron Inc.) is a ***115-kDa*** recombinant fusion protein." Ex.2049, ¶76-78 (citing Ex.1075, 403); *see also* Ex.2048, ¶87-91. In contrast, the molecular weight of aflibercept was routinely reported as 115 kDa. Ex.2049, ¶77 (citing Ex.2014, 596, Ex.2015, [0010]); *see also* Ex.2048, ¶88.

The POSA would have recognized that reported differences in molecular weights among VEGF Trap-Eye proteins, as well as those between the reported molecular weights of VEGF Trap-Eye and aflibercept, could reflect differences in the amino acid sequence. Ex.2049, ¶78; Ex.2048, ¶89-91. Thus, differences in reported molecular weights of "VEGF Trap-Eye," coupled with Dixon's generic description of "VEGF Trap-Eye" as having binding domains from human VEGFR1 and human VEGFR2 with a human IgG Fc, would support the conclusion that "VEGF Trap-Eye" referred to a genus of protein sequences that was not limited to the recited amino acid sequence. Ex.2049, ¶¶63-83; Ex.2048, ¶90-91. Moreover, equating aflibercept with "VEGF Trap," "VEGF Trap-Eye," and

"VEGF-Trap$_{R1R2}$,"[7] would not have suggested to the POSA that "VEGF Trap-Eye" corresponded to ***only*** aflibercept, but rather, may have suggested that "VEGF Trap-Eye," like "VEGF Trap" or "VEGF-Trap$_{R1R2}$," describes multiple different protein sequences. Ex.2049, ¶80.

In view of this conflicting prior art, Petitioner fails to establish that the term "VEGF Trap-Eye" was known to necessarily refer to the amino acid or nucleic acid sequence recited in the Challenged Claims.

c. None of Petitioner's references discloses that "VEGF Trap Eye" corresponds to only the recited sequence

Petitioner and Dr. Albini rely on various Regeneron patents and published

[7] Paper 1, 26 (citing Ex.Ex.1007) ("Aflibercept, VEGF Trap, VEGF Trap-Eye, VEGF-Trap$_{R1R2,}$ and AVE0005 are simply different names for the same molecule.").[8] As discussed in the POPR, Petitioner also relies on Regeneron's PTE Application (Ex. 1024), filed nearly a year after the priority date, to try to connect "VEGF Trap-Eye" to "aflibercept" (Paper 1, 27), but the meaning of "VEGF Trap-Eye" must be understood as the POSA would view the term as of the priority date without reference to how the term may have later changed. *See Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1354 (Fed. Cir. 2000) (holding a term is to be understood based on knowledge in the art as of the priority date, even if it later acquires a different meaning).

applications[8]—the '173 Patent (Ex.1008), '758 Patent (Ex.1010), '757 Patent (Ex.1022), '959 Patent (Ex.1023), '664 Patent (Ex.1010), and a Dix published patent application (Ex.1033)—to purportedly show correspondence between the recited VEGF antagonist fusion protein and amino acid sequences and sequences disclosed in the art. Paper 1, 26-27. The trouble with Petitioner's hindsight approach is that none of its cited patents identifies any of its disclosed sequences as "VEGF Trap-Eye" (or "aflibercept" for that matter) and other VEGF Trap sequences, including other VEGF-Trap$_{R1R2}$ sequences, were known in the art and published in some of those same references. Ex.2049, ¶¶69-74, 84-89; Ex.2130 (Albini Tr.), 325:21-326:17 (agreeing that no prior art Regeneron patent identifies the disclosed amino acid or nucleic acid sequences as "VEGF Trap-Eye"). Thus, disclosure of the recited sequences among other disclosed VEGF Trap sequences in

[8] As discussed in the POPR, Petitioner also relies on Regeneron's PTE Application (Ex. 1024), filed nearly a year after the priority date, to try to connect "VEGF Trap-Eye" to "aflibercept" (Paper 1, 27), but the meaning of "VEGF Trap-Eye" must be understood as the POSA would view the term as of the priority date without reference to how the term may have later changed. *See Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1354 (Fed. Cir. 2000) (holding a term is to be understood based on knowledge in the art as of the priority date, even if it later acquires a different meaning).

Petitioner's cited references would not have informed the POSA that VEGF Trap-Eye necessarily possessed the amino acid sequence or nucleic acid sequence of the Challenged Claims.

d. Regeneron consistently characterized "VEGF Trap-Eye" as an ophthalmology product and "aflibercept'" as an oncology drug

Regeneron publications, Dixon, and Heier-2009 consistently refer to Regeneron's ophthalmology drug as "VEGF Trap-Eye," and refer to Regeneron's oncology product as aflibercept. Ex.2048, ¶¶73-79 (showing consistent use of the term VEGF Trap-Eye for ophthalmology and aflibercept for oncology in clinical trial submissions, press releases, SEC filings, and scientific publications).

In its Institution Decision, the Board says: "Dixon discloses that a new drug for the treatment of age-related macular degeneration ("AMD") is aflibercept ("VEGF Trap-Eye"), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2." Paper 21, 14 (citing Ex.1006, Abstract). But Dixon does not say this. Rather, Dixon discloses that aflibercept is a promising new anti-VEGF agent:

> The advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD. In addition to two anti-VEGF drugs currently in widespread use, ranibizumab and bevacizumab, a number of medications that interrupt angiogenesis are currently under investigation. One promising new drug is aflibercept (VEGF Trap-Eye), a

> fusion protein that blocks all isoforms of VEGF-A and placental growth factors -1 and -2.

Ex.1006, Abstract. Then, in the next sentence, Dixon identifies the objective of the paper—to "review the current literature and clinical trial data regarding VEGF Trap-Eye for the treatment of neovascular AMD"—and identifies the results/conclusion as "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." *Id*. In contrast to its characterization of VEGF Trap-Eye as a novel anti-VEGF therapy in clinical trials for neovascular AMD, Dixon identifies aflibercept as an "oncology product." Ex.2049, ¶40; Ex.2048, ¶81; Ex.1006, 1575.

Indeed, Dr. Albini, Petitioner's expert, acknowledged that Regeneron consistently referred to VEGF Trap-Eye and aflibercept for different therapeutic indications and that it was "certainly possible" that the POSA reading Dixon could have concluded that VEGF Trap-Eye and aflibercept were different products. Ex.2130 (Albini Tr.), 334:20-335:9, 342:12-343:4. This is fatal to Petitioner's inherency assertion.

Moreover, the POSA would have known that Genentech's anti-VEGF oncology drug (Avastin®) had a different protein sequence than its anti-VEGF ophthalmology drug (Lucentis®), even though Avastin was used off-label in ophthalmology. Ex.2048, ¶¶82-85; *see also* Ex.2130 (Albini Tr.), 342:5-11. Specifically, the POSA would have known that Genentech modified its anti-VEGF

oncology drug to make it more compatible for ophthalmic administration. Ex.2048, ¶¶83-85. Thus, it would have been reasonable for the POSA to conclude that Regeneron's anti-VEGF oncology product, aflibercept, was different from its ophthalmology product, "VEGF Trap-Eye." Ex.2048, ¶86.

The mere possibility that "VEGF Trap-Eye" could include the recited amino acid or nucleic acid sequence is insufficient to demonstrate inherency for anticipation. *See Endo*, 894 F.3d at 1383; *see also In re Oelrich*, 666 F.2d at 581. Instead, each of Petitioner's references provide an "incomplete description" of VEGF Trap-Eye, thereby "denying skilled artisans from having access to" that claimed invention. *Id*. Thus, Petitioner has failed to establish that any of its Grounds 1-4 references necessarily discloses the amino acid or nucleic acid sequence of VEGF Trap-Eye. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055-56 (Fed. Cir. 2010).

VI. GROUND 4: PETITIONER FAILS TO ESTABLISH THAT CLAIMS 1 AND 8-12 ARE UNPATENTABLE BASED ON DIXON'S DISCLOSURE OF THE VIEW DOSING REGIMEN

Petitioner fails to carry its burden of demonstrating that any of the Challenged Claims is anticipated or rendered obvious by VIEW1/2 as disclosed by Dixon (Ground 4) for the reasons set forth in Section V and as further set forth below.

A. Petitioner Fails to Establish That the 8-Week Dosing Arm of the VIEW Clinical Trial Anticipates the Claimed PRN Dosing Regimen (All Challenged Claims)

In Ground 4, Petitioner argues that Dixon's disclosure of a prospective fixed

8-week dosing regimen (following three monthly doses) in VIEW1/2 anticipates the claimed PRN method of treatment. Paper 1, 53-58 (citing Ex.1006, 1576). But Dixon's VIEW1/2 disclosure fails to disclose a "tertiary dose" that "is administered on an as-needed/*pro re nata* PRN basis," as required by each of the Challenged Claims. Ex.2050, ¶131. Tellingly, Petitioner's claim chart does not purport to rely on Dixon for this limitation but instead relies on a tortured reading of the '069 Patent's prosecution history to argue that 8-week dosing and PRN dosing are the same thing. Paper 1, 55. Petitioner's argument is factually incorrect and legally unsound. Because Petitioner fails to show that Dixon discloses a critical limitation of each of the Challenged Claims, its Ground 4 anticipation challenge fails. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention ….").

Eight-week, fixed dosing (following three monthly doses), as described in Dixon, is ***not*** a disclosure of recited tertiary dosing "administered on an as-needed/*pro re nata* (PRN) basis." Ex.2050, ¶131; *see also* Ex.2130 (Albini Tr.), 285:15-286:3 (admitting that PRN dosing is more burdensome than eight-week fixed dosing). Accordingly, Dixon cannot anticipate the Challenged Claims of the '069 Patent because it does not disclose the claimed dosing regimen. *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either

expressly or inherently described, in a single prior art reference.").

Moreover, Petitioner's argument that 8-week dosing should mean the same thing as PRN dosing based on Regeneron's statements in prosecution is both factually incorrect and legally irrelevant to its Ground 4 argument *(i.e.*, what Dixon discloses). Paper 1, 55. During prosecution of the '069 Patent, Patent Owner did not describe VIEW's fixed, 8-week dosing regimen as a PRN regimen. Rather, Regeneron explained that the Heier 2012 reference showed that extended dosing regimens with VEGF Trap-Eye were unexpectedly non-inferior to the prevailing standard of care (*i.e.,* monthly injections of ranibizumab). Ex.1017, 136. Additionally, while Heier 2012 reports the clinical trial results from Year 1 of the VIEW1/2 trials, which tested fixed dosing regimens (including an 8-week dosing regimen), it also sets forth the clinical trial results for Year 2, which tested PRN dosing. Ex.1018, 10 ("The results of this second year were recently presented … and reveal … comparable visual acuity maintenance (91-92%) in each group at the 96-week time point"). Thus, by the time Heier 2012 published the clinical trial results for Year 2 of VIEW1/2, it was known that the second-year PRN dosing regimen resulted in extended dosing. *Id.* ("The total number of active injections (baseline to week 96) was 16.0 to 16.2 in the monthly intravitreal aflibercept groups … and 11.2 in the original 2q8 group.").[9] As a consequence, Regeneron's

[9] The actual mean number of injections in year 2 of VIEW was approximately four.

statements during prosecution that "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" were fully supported by Heier 2012. Ex.1017, 137.

More importantly, Regeneron's prosecution history statements about a different publication are not legally relevant to Petitioner's anticipation arguments regarding the Dixon reference in this IPR. Petitioner offers no authority for its suggestion that anticipation can be based on prosecution history estoppel rather than on prior art, and Regeneron is aware of none. Because Petitioner fails to make a *prima facie* case for anticipation, its Ground 4 challenge must be rejected.

B. Petitioner Fails to Establish That the 8-Week Dosing Arm of the VIEW Clinical Trial Renders Obvious the Claimed PRN Dosing Regimen (All Challenged Claims)

Petitioner argues that Dixon provides motivation to modify the Q8 dosing arm of VIEW by retaining three monthly loading doses but swapping out Q8 maintenance dosing for PRN dosing. Paper 1, 58. Petitioner argues that: (1) the POSA purportedly "routinely began therapy with three monthly loading doses and followed with PRN re-treatment" as in the PrONTO study; (2) Dixon demonstrated "positive results" for a study that involved four initial loading doses followed by administration of VEGF Trap-Eye on a PRN-basis; and (3) the VIEW1/VIEW2 trials incorporated a second year wherein PRN dosing was used. *Id.*, 58-59. Based on this, Petitioner argues that it would have been obvious to treat patients with the

recited VEGF antagonist using three loading doses followed by PRN maintenance dosing. *Id.* But Petitioner's obviousness argument relies on a fundamentally flawed hindsight-driven reconstruction of the Challenged Claims.

Without any explanation or basis, Petitioner assumes that the POSA would have selected the Q8 dosing regimen from among the three VEGF Trap-Eye arms as the starting point for its obviousness combination. Petitioner ignores that Dixon discloses that the prospective VIEW trials will study three dosing regimens for VEGF Trap-Eye—0.5Q4, 2Q4, and 2Q8 (following three monthly doses). Ex.2050, ¶131; Ex.1006, 4; *see also* Ex.2130 (Albini Tr.), 271:1-22. Only the 2Q8 dosing arm included three monthly loading doses; the other two VEGF Trap-Eye dosing arms used 12 monthly doses before commencing PRN dosing in the second year of VIEW. Ex.2130 (Albini Tr.), 272:1-10, 282:15-18. Petitioner must demonstrate that the POSA would be motivated to combine the teachings of the prior art to achieve the claimed invention. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016); *see also* 35 U.S.C. § 314(a). It has failed to do so.

Then, having handpicked the Q8 dosing arm to the exclusion of the other VIEW study arms, Mylan asserts that the POSA would have abandoned fixed Q8 maintenance dosing in favor of PRN dosing after the first three monthly loading doses. Again, Mylan fails to supply a reason for this modification. Moreover, an 8-week fixed maintenance dosing regimen (after three monthly loading doses), as

in the VIEW trials, requires patients to be seen by their physicians only when they are treated—*i.e.*, once every 8-weeks. Ex.2050, ¶¶132-134. In contrast, under a PRN treatment protocol, even if the patient is not treated at each visit, the patient is still required to visit his/her physician on a regular (*i.e.*, monthly) basis for monitoring. Ex.2050, ¶¶133-134; Ex.2130 (Albini Tr.), 278:22-279:11.

Indeed, Mylan's own expert, Dr. Albini, acknowledges that PRN dosing would be more burdensome than a Q8 maintenance dosing regimen:

> Q. PRN dosing would still require monthly office visits; correct?
>
> A. That's the common understanding. That's PRN protocol.
>
> Q. And as we discussed earlier, you know, maybe not all office visits are as long as the initial office visit, but you're still looking at probably 2 to 3 hours per office visit on a PRN schedule; correct?
>
> A. That's correct.
>
> ***
>
> Q. …Would you agree that regular interval dosing on a Q8 dosing regimen would be less burdensome than monthly PRN dosing?
>
> A. I -- I agree that it's -- it sounds certainly less burdensome.
>
> Q. It would be less burdensome; correct?

A. Yes.

Ex.2130 (Albini Tr.), 278:22-279:11, 285:15-286:3 (objections omitted). There is simply no basis to conclude that the POSA would have been motivated to modify the VIEW Q8 dosing regimen with a dosing regimen that would have been considered to be more burdensome. Ex.2130 (Albini Tr.), 285:15-286:3; Ex.2050, ¶¶133-138. "[T]he benefits, both lost and gained, should be weighed against one another. That is consistent with the longstanding principle that the prior art must be considered for all its teachings, not selectively." *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1331-32 (Fed. Cir. 2019) (affirming final IPR decision that claims were not proven invalid for obviousness where "[c]onsidering the prior art as a whole, we conclude that substantial evidence supports the Board's finding of no motivation to combine") (citations omitted); *see also AstraZeneca AB v. Aurobindo Pharma Ltd.*, 232 F. Supp. 3d 636, 646-47 (D. Del. 2017) (holding that the asserted patent claims were not obvious and finding that expert's testimony was flawed for failing to consider the prior art as a whole, but instead only "looked to a selection of prior art ***handpicked*** by [accused infringer's] counsel in order to select the compound for his obviousness analysis. This is evidence of classic hindsight bias.").

VII. GROUND 5: PETITIONER FAILS TO ESTABLISH THAT ANY CHALLENGED CLAIM IS RENDERED OBVIOUS BY HEIER-2009 IN VIEW OF MITCHELL OR DIXON

Petitioner fails to show that any Challenged Claim is rendered obvious by

Heier-2009 in combination with either Mitchell or Dixon and, optionally, either the '758 Patent or Dix (Ground 5).

A. Heier-2009 in View of Mitchell or Dixon Does Not Render Obvious Claims 1 and 8-12

Petitioner fails to carry its burden of demonstrating that any of the Challenged Claims are rendered obvious by Heier-2009 in combination with either Mitchell or Dixon and, optionally, either the '758 Patent or Dix. Petitioner relies on its argument "that the claimed amino acid and nucleic acid sequences are inherent features of VEGF Trap-Eye disclosed in both Heier-2009 and Dixon." Paper 1, 61 n.23. However, for the reasons set forth in Section V *supra*, Petitioner's argument fails.

Alternatively, Petitioner argues that 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." Paper 1, 61, n.23. But, as discussed above, neither the '758 patent nor the Dix application uses the term "VEGF Trap-Eye" (or aflibercept). And both disclose multiple VEGF Trap and VEGF $Trap_{R1R2}$ sequences, including VEGF $Trap_{R1R2}$ that do not satisfy the recited sequence limitations of the Challenged Claims. Petitioner fails to supply a reason, let alone any evidence, that the POSA would have selected the claimed sequences as opposed to the disclosed, unclaimed sequences. For example, the '758 Patent discloses Figures 21A-C and SEQ ID NO:11 and SEQ ID NO:12, which correspond to the nucleic acid sequence and amino acid sequence for Flt1D2.Flk1D3.FcΔC1(a).

Ex.1010, 10:4-6. The '758 Patent calls this protein sequence "R1R2," (Ex.1010, 26:13-15), but this disclosed VEGF Trap sequence does not satisfy the recited sequence limitations of the '069 Patent. Likewise, Dix discloses a SEQ ID NO: 1 and a SEQ ID NO:2, which correspond to a different disclosed VEGF Trap protein sequence that does not satisfy the sequence limitations of the Challenged Claims. None of Petitioner's arguments or evidence show why the POSA would have selected one of these disclosed VEGF Trap sequences over another.

B. Claim 8 Is Nonobvious for the Additional Reason That the POSA Would Not Have Been Motivated to Decrease the Number of Loading Doses from Four to Three Based on the CLEAR-IT 2 Data

Petitioner asserts that the POSA would have been motivated to modify Regeneron's Phase 2 CLEAR-IT 2 dosing regimen by reducing the number of loading doses from four monthly loading doses, as reported in Heier-2009,[10] to three loading monthly doses based on (a) ranibizumab dosing regimens, as reported in Mitchell, or (b) the prospective VIEW trial, as reported in Dixon. Paper 1, 65. Petitioner's assertions lack merit.

First, Petitioner ignores that the results of CLEAR-IT 2, particularly when

[10] As Dr. Albini acknowledges, the POSA would have understood Heier-2009 to disclose a total of 4 monthly loading doses followed by PRN (*i.e.*, an initial dose followed by three monthly loading doses), even though the text of Heier-2009 is not clear on this point. Ex1002, ¶¶96, n. 15.

combined with knowledge in the art as reflected in Mitchell, would have discouraged the POSA from dropping the fourth monthly loading dose. The POSA would have used monthly loading doses to dry the retina and maximize initial visual acuity gains before moving to a maintenance dosing approach, here PRN. Ex.2050, ¶141. For ranibizumab, the art taught that initial visual acuity gains and reduced CRT were achieved with three monthly loading doses. Ex.2050, ¶142. However, for VEGF Trap-Eye, a different molecule than ranibizumab, the CLEAR-IT 2 results taught that visual acuity gains and fluid on retina (as reported by CRT) ***continued to improve with the fourth monthly loading dose***. Ex.2050, ¶144-145 Thus, rather than providing any motivation or rationale to modify CLEAR-IT 2, the prior art would have actually ***discouraged*** the POSA from dropping the fourth monthly loading dose from a VEGF Trap-Eye dosing regimen. Ex.2050, ¶144.

Second, Petitioner uses hindsight to argue that the POSA would have selected three monthly loading doses from one of the dosing regimens tested in Regeneron's prospective Phase 3 trial, and combined it with the PRN maintenance dosing of Regeneron's Phase 2 CLEAR-IT trial. Once again, Petitioner fails to supply a reason that the POSA would have selected the 2Q8 arm of VIEW as opposed to the 0.5Q4 or 2Q4 dosing arms, which required 12 monthly loading doses before moving to a PRN schedule. Likewise, Petitioner fails to supply a reason for why the POSA, having selected the three monthly loading doses of the 2Q8 arm would have abandoned Q8 maintenance dosing and replaced it with PRN dosing, which was

known to be more burdensome. Ex.2130 (Albini Tr.), 285:15-286:3. At bottom, Petitioner works backwards from the claimed invention using improper hindsight to construct the claimed dosing regimen by picking and choosing at random from possible dosing regimens under investigation in the art.

Critically, Petitioner fails to identify any motivation to arrive at the claimed dosing regimen. Neither Petitioner nor Dr. Albini provides a motivation to explore fewer ***loading*** doses. Petitioner relies on statements in Dixon that—the "time and financial burden of monthly injections" led researchers to "examine the efficacy of alternative dosing schedules" and "it may be possible to extend the time between injections if the patient is frequently monitored"—for motivation to explore less frequent dosing. Paper 1, 32; Ex.1002, ¶¶76-77, 168. But Dixon's statements have nothing to do with reducing the number of initial monthly ***loading*** doses.[11] While

[11] Rather, the prior art upon which Dr. Albini relies consistently and repeatedly described a motivation to reduce the number of maintenance injections required to treat a chronic disorder. *See, e.g.*, Ex.1006, 1577 ("However, limitations of current therapy include the need for frequent intraocular injections, as often as monthly, ***without a defined stopping point***. Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis. A significant time and financial burden falls on patients ***during their treatment course***.") (emphases added); Ex.2050, ¶148. Eliminating a single loading dose

Dr. Albini points to Mitchell's statement that, "[p]rospective trials would be valuable for investigating fewer injections in the initiation phase," (Ex.1002, ¶106) he acknowledges that it was never done. Ex.2130 (Albini Tr.), 231:12-22. Indeed, every PRN trial that was conducted with ranibizumab in the prior art retained the three monthly loading doses that were required to maximize initial visual acuity and reduce CRT. Ex.2050, ¶146; Ex.1030, 6.

It is well-established, however, that the prior art must be considered for all that it teaches. *Impax Lab's. Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018) (holding that in an obviousness analysis, "prior art should be viewed as a whole."). Petitioner must identify "some kind of motivation … from some source, [to show] why a person of ordinary skill would achieve the patented invention." *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1367 (Fed. Cir. 2012) (quoting *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 (Fed. Cir. 2008)). Moreover, it is fundamental that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

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would do little, if anything, to reduce the patient's long-term treatment burden, particularly as compared to the reduction achieved through extended maintenance dosing. *Id*.

Petitioner must do more than explain that the two references could be combined; it must explain why the POSA would have been motivated to select and combine the references to arrive at the claimed invention. *Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993-94 (Fed. Cir. 2017); *Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) ("[O]bviousness concerns whether a skilled artisan not only ***could have made*** but ***would have been motivated to make*** the combinations or modifications of prior art to arrive at the claimed invention."). Here, Petitioner has done nothing more than show that Heier-2009 ***could*** have been combined with Mitchell or Dixon. Thus, the Board should reject Petitioner's Ground 5 challenge.

1. Ranibizumab Dosing Regimens as Reported in Mitchell

Mylan asserts that Mitchell would have motivated the POSA to use three monthly loading doses for VEGF Trap-Eye, rather than the four monthly loading doses disclosed in CLEAR-IT 2. Paper 1, 63-64. To the contrary, Mitchell taught that the optimal number of monthly loading doses depends on when the majority of patients experience the most initial visual acuity gains:

> Ranibizumab initiation with three consecutive monthly injections appears optimal as this was when the majority of patients experienced most VA [visual acuity] gain in all studies. Improvements occurred rapidly, and the largest VA gain occurred after the first injection.

Ex.1030, 4 (emphasis added). Mitchell notes that MARINA, ANCHOR, and the

active control arm of EXCITE were the only Phase 3 studies to use monthly injections of ranibizumab throughout the treatment period and observes that "[m]ost VA [visual acuity] improvement was seen during the initial 3-month phase with subsequent injections appearing to maintain the achieved benefit." *Id.*; Ex.2130 (Albini Tr.), 223:11-224:8; Ex.2050, ¶¶142, 146. Mitchell's Figure 2 illustrates this finding:

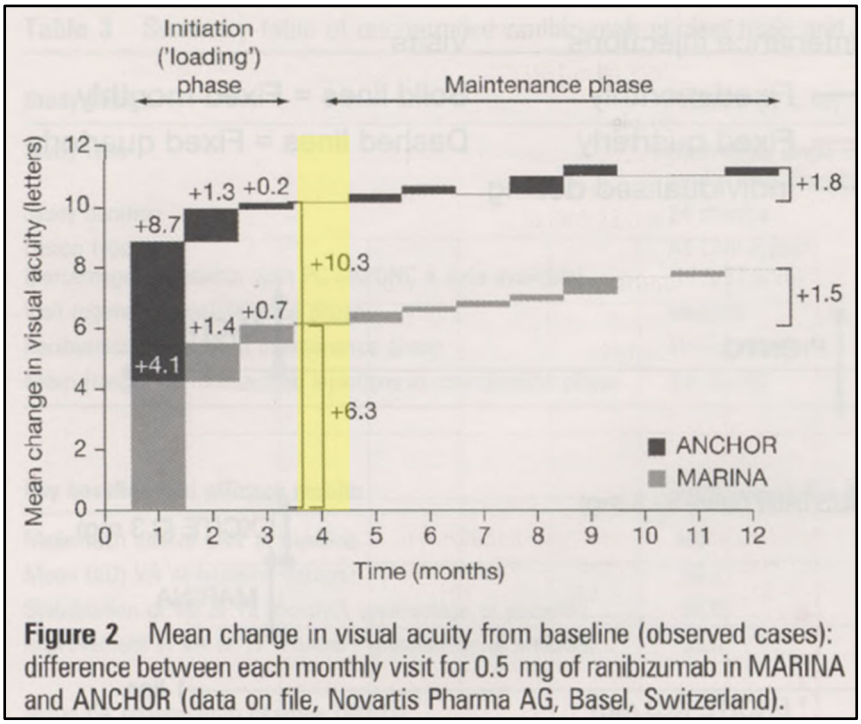


Figure 2 Mean change in visual acuity from baseline (observed cases): difference between each monthly visit for 0.5 mg of ranibizumab in MARINA and ANCHOR (data on file, Novartis Pharma AG, Basel, Switzerland).

Ex.1030, 7 fig. 2 (annotated with highlighting).

The clinical trial results of MARINA and ANCHOR showed no meaningful visual acuity benefit from a fourth monthly dose of ranibizumab. Ex.1030, Fig. 2; Ex.2050, ¶142. Indeed, Mylan's expert, Dr. Albini, acknowledges that a fourth monthly injection of ranibizumab provided only negligible visual acuity gain at

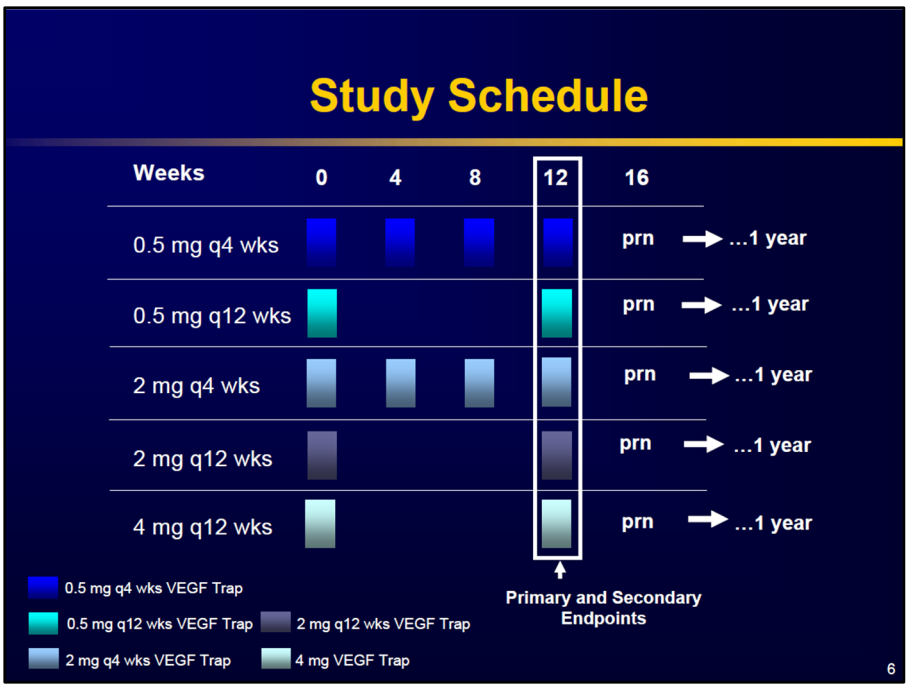
best. Ex.2130 (Albini Tr.), 230:15-21. On the basis of this "Level 1 evidence,"[12] Mitchell's clinical recommendation was that "0.5 mg of ranibizumab should be initiated with ***at least three*** consecutive monthly intravitreal injections, using an aseptic procedure." Ex.1030, 6 (emphasis added).

Contrary to Mylan's suggestion, Mitchell does not teach dropping a monthly loading dose: to the contrary, Mitchell makes clear that loading doses should be retained to maximize initial visual acuity gains. Ex.1030, 6, Fig. 2; Ex.2050, ¶¶142-146. Even the POSA that was motivated to explore less frequent dosing would have retained initial monthly loading doses to maximize initial visual acuity gains before moving to a maintenance dosing regimen that sought to extend the frequency of injections. Ex.2050, ¶¶147-149; Ex.2130 (Albini Tr.), 224:17-225:8; 233:17-21; 236:20-237:3; 244:10-12; *see also Impax Labs. Inc.*, 893 F.3d at 1379 (holding that in an obviousness analysis, "prior art should be viewed as a whole.").

The clinical trial results of CLEAR-IT 2 taught that the four monthly loading doses of VEGF Trap-Eye should be retained to maximize initial visual acuity gains and CRT reductions before moving to maintenance PRN dosing. Ex.2050, ¶¶144-145. CLEAR-IT 2 tested VEGF Trap-Eye on five different dosing arms. Two of the dosing arms tested four monthly loading doses followed by PRN and three arms

[12] Mitchell explains that Level I indicates "strong evidence (*e.g.*, well-designed, randomized, controlled clinical trials that address the issue in question). Ex.1030, 2.

tested quarterly dosing followed by PRN, as shown below:

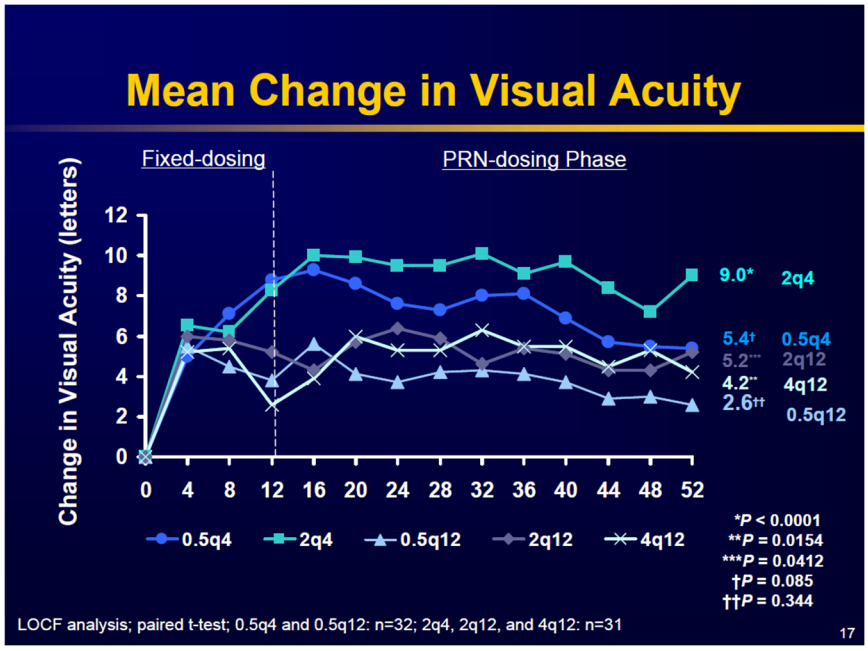


Ex.1055, 6; Ex. 2050, ¶121.

The CLEAR-IT 2 results demonstrated the importance of monthly loading doses in establishing the best visual acuity and anatomical outcomes. Ex.2050, ¶143. In particular, CLEAR-IT 2 showed the importance of the ***fourth monthly loading dose*** of VEGF Trap-Eye in maximizing initial visual acuity outcomes and CRT reduction. Importantly, subjects receiving monthly (Q4) dosing experienced improvements in both visual acuity and anatomical outcomes following the injection at week 12 (*i.e.*, at the fourth loading dose) as shown by the curves at week 16. Ex.2050, ¶144-145; Ex.1055, 17-18; Ex.2130 (Albini Tr.), 207:22-208:4; *see also* Ex.2028, 10, 12.

The week 16 results of CLEAR-IT 2 showed visual acuity improvement

following administration of a fourth loading dose (at week 12) for both monthly loading dose arms (0.5q4 and 2q4 arms):

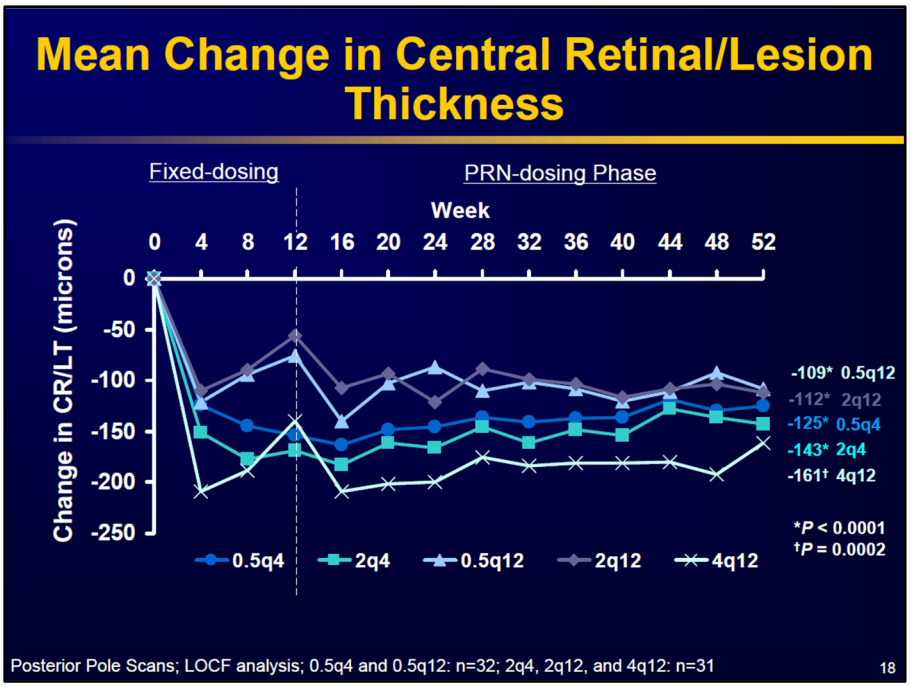


Ex.1055, 17; Ex.2050, ¶¶124-125, 144-145. Indeed, Mylan's expert, Dr. Albini, acknowledges that the fourth monthly loading dose resulted in visual acuity improvement:

> Q. Okay. So in CLEAR-IT 2, both of these monthly treatment arms show visual acuity improvement with the administration of the fourth monthly loading dose; correct?
>
> A. Correct.

Ex.2130 (Albini Tr.), 207:22-208:4. In fact, Dr. Albini concedes that visual acuity gains in CLEAR-IT 2 peaked after the administration of this fourth monthly loading dose. Ex.2130 (Albini Tr.), 208:5-11.

The CLEAR-IT 2 data also showed improvement in central retinal thickness (CRT) with the fourth monthly loading dose at week 16:



Ex.1055, 18; Ex.2050, ¶¶122-123, 144-145 Ex.2130 (Albini Tr.), 209:8-13. An increase in CRT corresponds with fluid re-accumulation on the retina and is a tell-tale sign that retreatment with an anti-VEGF agent is necessary. Ex.2130 (Albini Tr.), 211:1-5; Ex.2050, ¶122. Conversely, a decrease in CRT corresponds to drying of the retina and is generally associated with control over disease progression. Ex.1050, ¶¶143. CLEAR-IT shows that CRT reaches its lowest point for the monthly loading dose arms (0.5Q4 and 2Q4) after the fourth monthly loading dose. Ex.1050, ¶¶ 124, 144-145. Thus, the POSA reviewing CLEAR-IT 2 data would ***not*** have been motivated to drop the fourth monthly loading dose for VEGF Trap-Eye because CLEAR-IT 2 taught that the fourth monthly loading dose was

important to maximize initial visual acuity gains and anatomic improvements before moving to maintenance dosing. Ex.1050, ¶¶ 124, 144-145; *see also* Ex.1030, 6. Indeed, the visual acuity of subjects in the quarterly dosing arms of VEGF Trap-Eye never caught up to the visual acuity of subjects in the monthly loading dose arms, confirming the importance of using loading doses to maximize visual acuity gains before moving to a maintenance dosing regimen. Ex.2050, ¶¶144-146.

Contrary to Mylan's suggestion, Paper 1, 62, the POSA would not have considered modifying the CLEAR-IT 2 dosing regimen based on the PRN dosing regimens of Lucentis reported in Mitchell because the POSA would have known that ranibizumab (Lucentis) was a different molecule from the one being tested in CLEAR-IT 2. Ex.2050, ¶¶142-143 For example, when Genentech designed its Phase 3 trials of ranibizumab, it did not just copy the Q6 dosing regimen of Macugen. Ex.2050, ¶142. Likewise, when designing a PRN method of treatment using VEGF Trap-Eye, the POSA would have understood that differences between the two molecules would have made Lucentis PRN dosing regimens (three loading doses) less meaningful than the CLEAR-IT 2 dosing regimen (four loading doses). *Id.* In particular, the POSA would have understood that while three loading doses may have maximized visual acuity gains for ranibizumab, one would not necessarily

expect the same to hold true for VEGF Trap-Eye.[13] Ex.2050, ¶146.

Dr. Albini's opinion that the POSA would have been motivated to drop a loading dose from CLEAR-IT 2 is also contrary to conventional wisdom that monthly loading doses should continue until retina dryness and visual acuity gains have plateaued. Ex.2050, ¶141. The POSA would have used monthly loading doses to dry the retina and maximize initial visual acuity gains before moving to a maintenance dosing approach. Ex.2050, ¶¶141; Ex.1030, 4. For ranibizumab, the art taught that three monthly loading doses optimized initial visual acuity gains. Ex.2050, ¶142; Ex.1030, 4. The CLEAR-IT 2 results taught the importance of the fourth monthly loading dose. Consequently, the POSA would have been discouraged, not motivated, to modify the CLEAR-IT 2 dosing regimen by reducing the number of monthly loading doses from four to three. Petitioner does not explain why the POSA would have been motivated to pursue an ostensibly less efficacious treatment in order to save a single intravitreal injection over the course of treating a chronic disease.

2. Prospective View Dosing Regimens as Reported in Dixon

Next, Petitioner contends that the POSA would have been motivated to

[13] In fact, the results of PrONTO were reported before CLEAR-IT 2 began enrolling patients (Ex.2100, Ex.2101), even so Regeneron did not just routinely adopt three monthly loading doses for a PRN regimen for VEGF Trap-Eye.

combine the three monthly loading doses from the Q8 dosing arm of VIEW with PRN maintenance dosing from CLEAR-IT 2 to arrive at the recited dosing regimen of Claim 8. Paper 1, 61. Alternatively, Petitioner contends that the POSA would have been motivated to select the three monthly loading doses from the Q8 dosing arm in VIEW but then drop the Q8 dosing and proceed directly to the second year dosing schedule of PRN dosing. As discussed in Section VI.B. above, Petitioner fails to supply any motivation for its mix-and-match approach to piecing together the claimed dosing regimen from different elements of the prospective VIEW trial. *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (holding that "hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention" is not permissible.). And, indeed, "[c]are must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011); *see also Sanofi Aventis U.S., LLC v. Dr. Reddy's Lab'ys, Inc.*, 933 F.3d 1367, 1375 (Fed. Cir. 2019).

As discussed above in Section VI.B., Petitioner does not explain why the POSA would have selected the 2Q8 dosing arm of VIEW (after three monthly loading doses) from among the VIEW dosing arms. And then, having selected that arm, why the POSA would jettison Q8 dosing and proceed immediately to PRN dosing of the second year of VIEW.

It is Petitioner's burden to show that the POSA would have been motivated to combine the teachings of the prior art to achieve the claimed invention. *Intelligent Bio-Sys., Inc.*, 821 F.3d at 1367-1368 ; *see also* 35 U.S.C. § 314(a). Petitioner must supply a motivation to replace VIEW's fixed, 8-week maintenance dosing regimen with PRN dosing, which requires patients to make monthly monitoring visits to their physician. *See Henny Penny Corp.*, 938 F.3d at 1331-32 ("[T]he benefits, both lost and gained, should be weighed against one another. That is consistent with the longstanding principle that the prior art must be considered for all its teachings, not selectively."). Moreover, it is undisputed that PRN dosing was known to be more burdensome than fixed, 8-week dosing. Ex.2130 (Albini Tr.), 278:22-279:11, 285:15-286:3; Ex.2050, ¶¶133-135; *see also* Ex.1006, 1574 ("However, even with the p.r.n. dosing utilized in the PrONTO study, patients are still required to make monthly visits to the office with frequent and expensive testing."). Petitioner's picking-and-choosing of certain elements of the VIEW dosing arm is based on impermissible hindsight and the undisputed evidence demonstrates that the POSA would ***not*** have been motivated to replace extended, 8-week fixed dosing with PRN dosing to arrive at the claimed dosing regimen. Ex.2050, ¶¶131-38; Ex.2130 (Albini Tr.), 278:22-279:11, 285:15-286:3. Consequently, Petitioner's Ground 5 challenge fails.

VIII. CONCLUSION

For the foregoing reasons, Patent Owner respectfully requests that the Board

affirm the validity of the Challenged Claims of the ’069 Patent.

Dated: February 11, 2022

Respectfully Submitted,

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this Patent Owner Response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This Patent Owner Response (including figure labels and annotations) contains 9,336 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it.

The undersigned further certifies that this Patent Owner Response complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This Patent Owner Response has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14-point font.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq*., the undersigned Certifies that on February 11, 2022, a true and entire copy of this **PATENT OWNER RESPONSE**, and all supporting exhibits, were served via e-mail to the Petitioners at the following email addresses:

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