UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Inter Partes Review No.: IPR2023-00532

U.S. Patent No. 10,130,681 B2
Filed: March 28, 2017
Issued: November 20, 2018
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. 10,130,681 B2

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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")
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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 HealthCare 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),

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	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	IPR2021-00881 Ex.1109, Diana V. Do Deposition Transcript (April 21, 2022) ("IPR2021-00881 Ex.1109")
1017	File History of U.S. Patent No. 10,130,681 B2 ("'681 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	IPR2021-00881 Ex.2051, Expert Declaration of Dr. Diana V. Do, M.D. ("IPR2021-00881 Ex.2051")
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	IPR2021-00881 Ex.1110, David M. Brown Deposition Transcript (April 26, 2022) ("IPR2021-00881 Ex.1110")
1023	File History for U.S. Patent No. 7,070,959, 12/22/2011 Patent Term Extension Application ("'959 FH, 12/22/2011 PTE")
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 1368 (2010) ("Engelbert-2010")
1026	John S. Rudge et al., *VEGF Trap Complex Formation Measures Production Rates of VEGF, Providing a Biomarker for Predicting Efficacious Angiogenic Blockade*, 104 PNAS 18363 (2007) ("Rudge-2007")
1027	Richard F. Spaide et al., *Prospective Study of Intravitreal Ranibizumab as a Treatment for Decreased Visual Acuity Secondary to Central*

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	Retinal Vein Occlusion, 147 AM. J. OPHTHALMOLOGY 298 (2009) ("Spaide")
1028	IPR2021-00881 Ex.2080, Jeffery S. Heier, *VEGF Trap-Eye for Exudative AMD*, RETINAL PHYSICIAN, Apr. 2009 ("IPR2021-00881 Ex.2080")
1029	Candelaria Gomez-Manzano et al., *VEGF Trap Induces Antiglioma Effect at Different Stages of Disease*, 10 NEURO-ONCOLOGY 940 (2008) ("Gomez-Manzano")
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	Polly A. Quiram & Yahui Song, *Exudative Age-Related Macular Degeneration: Current Therapies and Potential Treatments*, 1 CLINICAL MEDICINE: THERAPEUTICS 1003 (2009) ("Quiram")
1032	Press Release, Bayer AG, Bayer and Regeneron Start Additional Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration (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	Hamish M. Fraser et al., *The Role of Vascular Endothelial Growth Factor and Estradiol in the Regulation of Endometrial Angiogenesis and Cell Proliferation in the Marmoset*, 149 ENDOCRINOLOGY 4413 (2008) ("Fraser")
1037	CENTER FOR DRUG EVALUATION & RESEARCH, BLA No. 125156, Lucentis Medical Review ("Lucentis MR")
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1039	U.S. Patent No. 7,378,095 B2 ("'095 patent")
1040	Heinrich Heimann, *Intravitreal Injections: Techniques and Sequelae*, *in* MEDICAL RETINA 67 (Frank G. Holtz & Richard F. Spaide eds. 2007) ("Heimann-2007")

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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	CENTER FOR DRUG EVALUATION & RESEARCH, BLA No. 125-387, Eylea Medical Review ("Eylea MR")
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*

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	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	Rama D. Jager, *Risks of Intravitreous Injection: A Comprehensive Review*, 24 J. RETINAL & VITREOUS DISEASE 676 (2004) ("Jager-2004")
1058	Philip J. Rosenfeld et al., *Ranibizumab for Neovascular Age-Related Macular Degeneration*, 355 N. ENG. J MED. 1419 (2006) ("Rosenfeld-2006")
1059	Erik Christensen, *Methodology of Superiority vs. Equivalence Trials and Non-Inferiority Trials*, 46 J. HEPATOLOGY 947 (2007) ("Christensen")
1060	Jorma B. Mueller & Christopher M. McStay, *Ocular Infection and Inflammation*, 26 EMERGENCY MED. CLINICS N. ASM. 57 (2008) ("Mueller")
1061	Curriculum Vitae of Dr. Mary Gerritsen ("Gerritsen CV")

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1062	European Patent No. 2 663 325 (published as WO 2012/097019 A1) ("EP-325")
1063	File History of European Patent No. 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	European Patent No. 3 222 285 ("EP-285")
1067	File History of European Patent No. 3 222 285 ("EP-285-FH")
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://investor.regeneron.com/news-releases/news-release-details/enrollment-completed-regeneron-and-bayer-healthcare-phase-3?ReleaseID=408872 ("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")
1071	U.S. Patent No. 9,254,338 ("'338 patent")
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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	Kirk R. Wilhelmus, *The Red Eye, Infectious Conjunctivitis, Keratitis, Endophthalmitis, and Periocular Cellulitis*, 2 INFECTIOUS DISEASE CLINICS N. AM. 99 (1988) ("Wilhelmus-1988")
1083	Christopher Wirbelauer, *Management of the Red Eye for the Primary Care Physician*, 119 AM. J. MED. 302 (2006) ("Wirbelauer-2006")
1084	IPR2021-00881 Ex. 2055, Napoleone Ferrara et al., *Development of Ranibizumab, an Anti-Vascular Endothelial Growth Factor Antigen*

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	Binding Fragment, as Therapy for Neovascular Age-Related Macular Degeneration, 26 RETINA 859 (2006) ("IPR2021-00881 Ex. 2055)"
1085	IPR2021-00881 Ex.2050, Expert Declaration of David M. Brown, M.D. ("IPR2021-00881 Ex.2050")
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1088	Quan Dong Nguyen et al., *A Phase I Trial of an IV-Administered Vascular Endothelial Growth Factor Trap for Treatment in Patients with Choroidal Neovascularization due to Age-Related Macular Degeneration*, 113 OPHTHALMOLOGY 1522 (2006) ("Nguyen-2006")
1089	Press Release, Regeneron, Regeneron and Bayer HealthCare Announce VEGF Trap-Eye Achieved Durable Improvement in Vision Over 52 Weeks in a Phase 2 Study in Patients with Age Related Macular Degeneration (Aug. 19, 2008), https://investor.regeneron.com/news-releases/news-release-details/regeneron-and-bayer-healthcare-announce-vegf-trap-eye-achieved?ReleaseID=394056 ("Regeneron (19-August-2008)")
1090	IPR2021-00881 Ex.2103, Ongoing Treatment for Patients with Neovascular AMD, Retinal Physician (Oct. 1, 2007), https://www.retinalphysician.com/issues/2007/october-2007/ongoingtreatment-for-patients-with-neovascular-am ("IPR2021-00881 Ex.2103")
1091	John S. Rudge et al., CLINICAL DEVELOPMENT OF VEGF TRAP, *in* ANGIOGENESIS (William D. Figg & Judah Folkman eds. 2008) ("Rudge-2008")
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1094	Eugene S. Kim et al., *Potent VEGF Blockade Causes Regression of Coopted Vessels in a Model of Neuroblastoma*, 99 PROC. NAT'L ACAD. SCI. 11399 (2002) ("Kim")

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1095	File History of U.S. Patent No. 9,254,338 B2 ("'338 FH")
1096	U.S. Patent No.: 10,888,601 B2 ("'601 patent")
1097	U.S. Patent Nos. 7,303,746 B2; 7,303,747 B2; 7,306,799 B2; and 7,521,049 B2 ("Monthly-Dosing-Patents")
1098	IPR2021-00881, Ex.2003, Lucentis (ranibizumab injection) Label, revised June 2010 ("IPR2021-00881, Ex.2003")

Celltrion 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, 3-11, 13-14, 16-24, and 26 (the "Challenged Claims") of U.S. Patent No. 10,130,681 ("'681 patent") (Ex.1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc. ("Regeneron" or "PO").

I. INTRODUCTION.

The Challenged Claims mimic those in Regeneron's U.S. Patent No. 9,254,338 ("'338 patent") (IPR2021-00881), and like those claims, never should have issued. They are drawn to "VEGF Trap-Eye" dosing regimens well known to the person of ordinary skill in the art (hereafter, "POSA") long before January 2011. Regeneron's age-related macular degeneration ("AMD") Phase 3 clinical trials (VIEW1/VIEW2) with EYLEA® (a/k/a VEGF Trap-Eye or aflibercept) were designed to use the precise dosing regimens now covered by the Challenged Claims. The problem: Regeneron publicly disclosed these exact dosing regimens to POSAs as early as 2008. Aware of these invalidating disclosures, Regeneron sought to distinguish the Challenged Claims by incorporating a subset of the VIEW trials' "exclusion criteria," but, as discussed herein, the added elements do not save the Challenged Claims from the prior art, which renders them unpatentable.

Petitioner thus files this Petition, supported by expert declarations from Dr. Thomas Albini—a renowned ophthalmologist (Ex.1002), and Dr. Mary Gerritsen—a pharmacologist with over thirty years' experience (Ex.1003).

Anticipation. Each Challenged Claim is anticipated. VEGF Trap-Eye was a known blocker of vascular endothelial growth factor ("VEGF") and extensively disclosed in the prior art, including in each of Petitioner's asserted references. The amino acid and nucleotide sequences of VEGF Trap-Eye were independently disclosed and patented (*see* Ex.1008; Ex.1009; Ex.1010) well before the alleged priority date.

The VIEW1/VIEW2 clinical trials—including the VEGF Trap-Eye dosing regimens used therein—were widely published in numerous, fully-enabled prior art references. These publications disclosed *all* elements of the dosing regimen(s) in the Challenged Claims—most notably, administering three monthly loading doses followed by additional bi-monthly (*i.e.*, every-8-week) doses. Moreover, the "exclusion criteria" recited in the Challenged Claims are not entitled to patentable weight as such are widely-known requirements of the claimed and prior art dosing regimens. Notwithstanding, the VIEW1/VIEW2 clinical trials incorporated such exclusion criteria, and therefore, the added claim elements are inherently disclosed in Petitioner's asserted prior art.

Obviousness. The Challenged Claims are also invalid as obvious. As stated, the dosing regimen and exclusion criteria elements were all disclosed, either expressly or inherently, in Petitioner's asserted prior art—e.g., the recited exclusion criteria reflect general intravitreal injection guidelines and are nearly identical to those used in the Lucentis (ranibizumab) clinical trials. In addition, prior to January 2011, the VEGF Trap-Eye amino acid sequence (claim 1, 3rd wherein clause) and nucleic acid sequence (claim 14, 3rd wherein clause) were already patented, known, and widely disclosed to POSAs.

Separately, prior to January 2011, POSAs were strongly motivated to pursue anti-VEGF dosing schedules that were less frequent than monthly administration. In particular, the prior art extensively demonstrates the various burdens of monthly intravitreal injections to treat angiogenic eye disorders. (*See, e.g.*, Ex.1006, 1574). Combined with the abundance of positive, prior art data from Regeneron's clinical trials, a POSA would have reasonably expected success at treating angiogenic eye disorders with the claimed dosing regimens.

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

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

Petitioner identifies the following real parties-in-interest: Celltrion, Inc.; Celltrion Healthcare Co. Ltd.; and Celltrion Healthcare U.S.A., Inc. 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).

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

The '681 patent is currently being challenged in *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01225 (P.T.A.B.), instituted on January 11, 2023. The instant petition is concurrently filed with *Celltrion, Inc. v. Regeneron Pharms.*, *Inc.*, IPR2023-00533 (P.T.A.B.), challenging U.S. Patent No. 10,888,601 ("'601 patent"). The '601 patent is currently being challenged in *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226 (P.T.A.B.), also instituted on January 11, 2022.

In May 2021, Mylan filed petitions requesting IPR of two patents in the same family as the '681 patent. U.S. Patent No. 9,669,069 and U.S. Patent No. 9,254,338 are the subject of IPR2021-00880 and IPR2021-00881, respectively. The Patent Trial and Appeal Board ("Board") granted those petitions. (IPR2021-00880, Paper 21 (Nov. 10, 2021); IPR2021-00881, Paper 21 (Nov. 10, 2021). Celltrion filed petitions and moved for joinder in both of those cases (IPR2022-00257 and IPR2022-00258 respectively), which motions were granted on February 9, 2022. The Board cancelled all of the challenged claims in both of those proceedings, and Regeneron filed Notices of Appeal on January 10, 2021.

To the best of Petitioner's knowledge, the following are judicial or administrative matters that would affect, or be affected by, a decision in this proceeding: *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.) and *Horizon Healthcare Servs., Inc. v. Regeneron Pharms., Inc.*, No. 1:22-cv-10493-FDS (D. Mass.). Petitioner further identifies *Chengdu Kanghong Biotechnology Co. v. Regeneron Pharms., Inc.*, No. PGR2021-00035 (P.T.A.B.).

U.S. Patent Nos. 9,254,338 B2; 9,669,069 B2; 10,857,205 B2; 10,828,345 B2; 10,888,601 B2; and 11,253,572 B2; and U.S. Patent Application Nos. 17/072,417; 17/112,063; 17/112,404; 17/350,958; and 17/740,744 each claim the benefit of the '681 patent's purported priority date.

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

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Petitioner hereby consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below. A power of attorney accompanies this petition. Email: lgreen@geminilaw.com;

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III. PAYMENT 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 23-2415.

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

Petitioner certifies that the '681 patent—which issued on November 20, 2018—is available for IPR and that Petitioner is not barred or estopped from requesting IPR of the Challenged Claims on the grounds identified herein. Neither Petitioner nor any RPI has filed a civil action challenging the validity, or been served with a complaint alleging infringement, of the '681 patent more than one year prior to the filing of this Petition. *See Motorola Mobility LLC v. Arnouse*, No. IPR2013-00010, 2013 WL 12349001, *3 (P.T.A.B. Jan. 30, 2013).

V. 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.

VI. 35 U.S.C. § 325(d) DISCRETIONARY DENIAL IS UNWARRANTED.

Any argument that Petitioner's grounds or asserted prior art are cumulative of the '681 patent's prosecution should be rejected. As set forth below, the record confirms that the Examiner either (1) was not presented with the same or substantially the same art or arguments as Petitioner's, or (2) materially erred in allowing the Challenged Claims. *Advanced Bionics, LLC v. Med-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292, at *3-4 (P.T.A.B. Feb. 13, 2020) (precedential) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017)).

***Becton, Dickinson* Factors (a) and (b)**. Neither "the same [nor] substantially the same" art or arguments were previously presented to the Office during prosecution of the Challenged Claims. PO will likely argue that Dixon, NCT-795, and NCT-377 were submitted to the Office and marked "considered" by the Examiner. First, with respect to Dixon, the intrinsic record confirms, as the Board in IPR2021-00880 held, that "the disclosure[s] of Dixon that form the basis of Petitioner's Grounds...were not before the Examiner as prior art during examination (because the relevant disclosures were missing or omitted)." IPR2021-00880, Paper No. 21, 13, 10-13 (explaining that PO disclosed only a one-page version of Dixon to the Examiner and thus "[i]t would consequently have been impossible for the Examiner to analyze the limitations of the challenged claims in view of the complete

teachings of Dixon").[1] Moreover, as set forth in more detail below, Dixon provides extensive disclosures that do not appear in any of the art before the Examiner.

Second, although PO identified NCT-795 and NCT-377 on an IDS along with over 50 other references, neither were cited or relied upon by the Examiner.[2] Indeed, the only fact PO can point to is that Dixon (one page), NCT-795, and NCT-377 were disclosed; however, "[t]he Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, 62 (P.T.A.B. Aug. 30, 2019)

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[1] The '681 patent is a direct continuation of the '069 patent. (Ex.1001, Cover Page). During prosecution, PO incorporated by reference its disclosures from the '069 patent prosecution, telling the Examiner that "[a]ll of the references identified herein were disclosed in parent application serial number 14/972,560, and as such, only a copy of non-publication number (2) is attached." (Ex.1017, 5/26/2017 Transmittal Letter, 1). In other words, only the one-page version of Dixon was disclosed to the '681 patent Examiner. IPR2021-00880, Paper No. 21, 10-13.

[2] While IDS's were marked "considered," there is no evidence regarding the extent the Examiner considered NCT-795 and NCT-377 or whether the Examiner appreciated or understood their disclosures' relevance to the claims.

(citing *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, Paper 8, 40 (P.T.A.B. Nov. 7, 2018); *Amazon.com*, *Inc*. *v. M2M Solutions LLC*, IPR2019-01205, Paper 14, 16 (P.T.A.B. Jan. 27, 2020). In short, Petitioner's asserted art was neither "involved" nor "evaluated" during prosecution, and therefore, the prior art herein is not substantially the same as that previously were disclosed in parent application serial number 14/972,560, and as such, only a copy of non-publication number (2) is attached." (Ex.1017, 5/26/2017 Transmittal Letter, 1). In other words, only the one-page version of Dixon was disclosed to the '681 patent Examiner. IPR2021-00880, Paper No. 21, 10-13. considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. § 325(d).

Becton, Dickinson **Factor (d)**. Additionally, there is no overlap between Petitioner's arguments and those made during prosecution. None of Petitioner's grounds rely on prior art that was actually applied against the claims or discussed by the Examiner. *Amazon.com*, IPR2019-01205, Paper 14, 16 (finding that "a reference that 'was neither applied against the claims nor discussed by the Examiner' does not weigh in favor of exercising the Board's discretion under § 325(d) to deny a petition.")). More specifically, not one VIEW prior art reference (e.g., Dixon, NCT-795, or NCT-377) was applied against the pending claims or discussed by the Examiner. In fact, the Examiner did not assert any § 102 or § 103 rejections. (Ex.1017). Instead, the Examiner asserted obviousness-type double patenting

(OTDP) rejections (based upon Regeneron's earlier sequence patents) before allowing the claims, and therefore, there is no evidence to suggest Dixon (one-page version), NCT-795 or NCT-377 were substantively considered. (Ex.1017). In response to the OTDP rejections, Regeneron relied on ***post***-art disclosures of VIEW every-8-week dosing (Heier-2012), but withheld from the Examiner that the same regimen was disclosed in numerous prior art references. (Ex.1017, 6/25/2018 Remarks, 8-11).

Becton, Dickinson **Factors (c), (e), (f): Alternatively, The Examiner Erred**. As explained above, the answer to *Advanced Bionics*' first inquiry—whether the same or substantially the same art or arguments were previously presented to the Office—is a definitive "no." Accordingly, an allegation of Examiner error is unnecessary. Nonetheless, to the extent the Board disagrees and determines *Becton, Dickinson* factors (a), (b), and (d) are satisfied with respect to Dixon, NCT-795, and/or NCT-377, discretionary denial still is not warranted because the Examiner must have therefore overlooked each reference's anticipatory disclosures, constituting material error. *Advanced Bionics*, IPR2019-01469, Paper 6, 10 (listing silence as evidence of error). As stated above and in more detail below, Dixon, NCT-795, and NCT-377 disclose, either expressly or inherently, every element of the Challenged Claims. Consequently, the Examiner should have (at least) rejected the pending claims under §§ 102, 103.

Petitioner's Additional Evidence and Arguments. Finally, the Examiner did not have the benefit of the additional evidence and arguments Petitioner presents to the Board, further weighing against § 325(d) denial. For example, Petitioner provides expert declarations (Ex.1002; Ex.1003) that set forth the POSA's understanding of the prior art disclosures. *Guardian Indus. Corp. v. Pilkington Deutschland AG*, IPR2016-01635, Paper 9, 9-10 (P.T.A.B. Feb. 15, 2017); *Taro Pharms. U.S.A., Inc. v. Apotex Techs., Inc.*, IPR2017-01446, 2017 WL 6206129, at *8 (P.T.A.B. Nov. 28, 2017) (declining to deny petition under § 325(d) where petitioner presented new declaration evidence); *Tandus Flooring, Inc. v. Interface, Inc.*, IPR2013–00333, 2013 WL 8595289, at *2 (PTAB Dec. 9, 2013) (Paper 16) (same).

Petitioner also asserts six additional references never submitted (nor considered) during prosecution that provide additional, non-cumulative disclosures: Adis, Regeneron (8-May-2008), '758 patent, Dix, Rosenfeld-2006, and Heimann-2007. Likewise, Petitioner's anticipation and obviousness arguments were not considered by the Examiner. In sum, the '681 patent claims would not have been allowed had the Office considered the evidence and arguments presented herein.

VII. OVERVIEW OF PETITIONER'S CHALLENGES AND REQUESTED RELIEF.

A. STATUTORY GROUNDS OF CHALLENGE.

The following references anticipate the Challenged Claims:

Ground	Proposed Rejections (35 U.S.C. § 102)
1	Dixon
2	Adis
3	Regeneron (8-May-2008)

In addition, at least the following render the Challenged Claims obvious:

Ground	Proposed Rejections (35 U.S.C. § 102)
4	Dixon alone or in view of the ’758 patent and/or the ’173 patent
5	Dixon in combination with Rosenfeld-2006, and if necessary, the ’758 patent and/or the ’173 patent
6	Dixon in combination with Heimann-2007, and if necessary, the ’758 patent and/or the ’173 patent

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

VIII. OVERVIEW OF THE '681 PATENT.[3]

The '681 patent confirms angiogenic eye disorders, such as AMD, were known to be effectively treated through vascular endothelial growth factor("VEGF")[4] inhibition. (Ex.1001, 1:27-55). Indeed, prior to January 2011, ranibizumab (LUCENTIS®), an anti-VEGF agent, was FDA-approved for monthly administration via intravitreal injection to treat angiogenic eye disorders, including AMD. (*Id.*, 1:52-55; Ex.1048, 1). However, despite being approved for monthly dosing, ranibizumab was often administered on a *pro re nata* ("PRN" or "as needed") basis. Indeed, Genentech's ranibizumab clinical trials tested extended dosing, including PRN, and established that such regimens could achieve similar outcomes with fewer injections than monthly dosing. (Ex.1030, 1, 5).

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[3] Solely for this IPR, Petitioner assumes a January 13, 2011 priority date. Petitioner reserves all rights to challenge that date. The '681 patent is subject to the AIA given the inclusion of new matter in the Continuation-In-Part Application No. 13/940,370, now the '338 patent, filed July 12, 2013 (see IPR2021-00881).

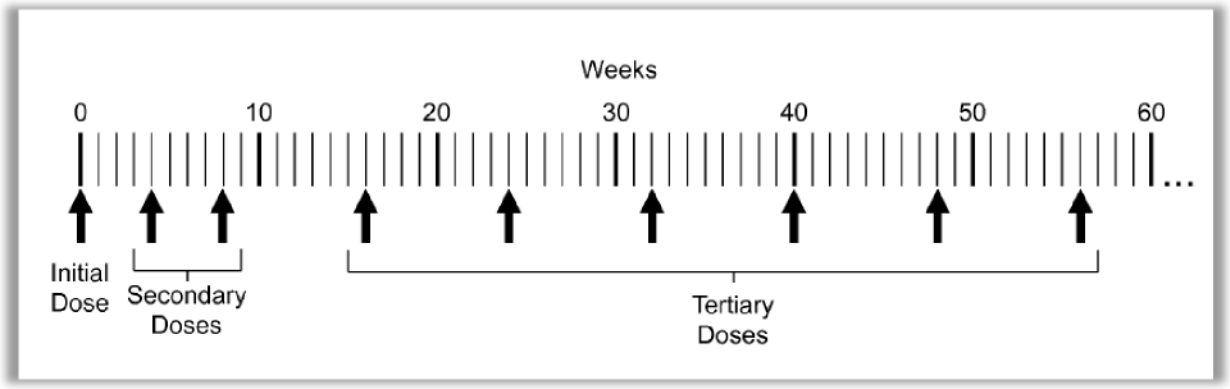
[4] VEGF is a "naturally occurring glycoprotein in the body that acts as a growth factor for endothelial cells." (Ex.1011, 711; Ex.1043, 627-28 (VEGF-A activity linked to ocular diseases, e.g., AMD).

Bevacizumab (AVASTIN®), another prior art anti-VEGF agent, has never been FDA approved for ocular indications, but has been used off-label to treat angiogenic eye disorders since long before January 2011. (Ex.1002, ¶64). Bevacizumab (AVASTIN®) is also most often administered on an as-needed (PRN) basis to treat angiogenic eye disorders. (Ex.1047, 8; Ex. 1039, 24-25). Notwithstanding, the '681 patent purports a need in the art for regimens that allow less frequent dosing. (Ex.1001, 1:56-62).

The '681 patent broadly claims dosing regimens for treating angiogenic eye disorders, including AMD, in patients not meeting any of three exclusion criteria: **(i)** active intraocular inflammation, **(ii)** active ocular or periocular infection, or **(iii)** ocular or periocular infection within two weeks prior to treatment, via: **(1)** administering a single initial dose of a VEGF antagonist (VEGF Trap-Eye), followed by **(2)** one or more "secondary doses" administered two to four weeks after the immediately preceding dose, followed **(3)** by one or more "tertiary doses" administered at least eight weeks apart. (*Id.*, 21:40-63 (Claim 1)). The '681 patent also specifically claims the prior art VIEW1/VIEW2 regimen, which eventually became FDA-approved for EYLEA® (*i.e.*, VEGF Trap-Eye/aflibercept). (*Id.*, 3:60-67, 22:39-44, 23:28-24:2). The '681 patent also claims variations of three of the thirty-seven exclusion criteria for the prior art VIEW1/VIEW2 clinical trials: "18. Active intraocular inflammation in either eye. 19. Active ocular or periocular

infection in either eye. 20. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye." (*Id.*, 11:38-41, 21:58-62; *id.*, 10:58-12:15). The exclusion criteria are mentioned only once in the specification (Example 4). (*Id.*, 9:14-13:59).

This VIEW1/VIEW2 dosing regimen is described in the specification as "an exemplary dosing regimen of the present invention" and is depicted graphically as follows:



(*Id.*, (Fig.1), 4:2-4, 2:55-62). The Figure, in combination with the three exclusion criteria listed above, illustrates and exemplifies a dosing regimen falling within the Challenged Claims.

During prosecution, PO argued, in response to OTDP rejections, that the (then-pending) claims were patentably distinct from its Monthly-Dosing Patents[5] on the ground that those did not disclose the claimed regimen. (Ex.1017, 6/25/2018 Remarks, 7). PO further argued once-per-month dosing represented the standard of care for treatment of AMD at the time of the invention and that the pending claims were distinct because an infinite number of other treatment protocols could have been considered. (*Id.*, 7-11; Ex.1018, 2537).

PO notably told the Examiner that Example 5 "illustrates an administration regimen encompassed by [issued claims 1 and 14] (*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 (DME)." (Ex.1017, 6/25/2018 Response, 10). One Example 5 dosing regimen is identical to the prior art VIEW1/VIEW2 regimen for AMD. The Example 5 Phase 2 DME dosing regimens also were disclosed before January 2011. (Ex.1068, 1).

[5] 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. (Ex.1097; Ex.1017, 4/3/2018 Office Action, 3-6).

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). Petitioner and expert declarant, Dr. Albini, have applied this standard.

A. "A METHOD FOR TREATING AN ANGIOGENIC EYE DISORDER IN A PATIENT."

1. The "method for treating" preamble is not a limitation and therefore does not require construction.

The "method for treating" preamble of independent claims 1 and 14 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[6] nor gives life, meaning or vitality to the claimed dosing regimen, and thus, it is not a limitation. *Bio-Rad*

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

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 Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (preamble 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 the intrinsic record here suggests otherwise. For example, there is no evidence PO asserted the preamble to traverse any Examiner rejections. (*See, e.g.*, Ex.1017, 6/25/18 Remarks, 7-11).

Moreover, PO's reliance on alleged "unexpected results" during prosecution does not render the preamble 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); *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).

For these reasons, Petitioner submits that the preamble is non-limiting and no construction is necessary.

2. PO's anticipated argument that the preamble is a positive limitation should be rejected.

In related proceedings, PO has argued that analogous preambles (in patents within the same family) are positive claim limitations but PO provides a variety of proposals for that same term:

- "a therapeutically effective method," (PGR2021-00035, Paper 6, 7);
- "an effective method of treatment," (IPR2021-00881, Paper 10, 36);
- "a high level of efficacy that is not inferior to the existing standard-of-care," (IPR2021-00881, Paper 41, 12); and
- "Regeneron does not advance claim construction positions for these terms," (IPR2021-00880, Paper 10, 19).

It remains to be seen which of these approaches PO will assert here, or if they will submit something new. Regardless, any attempt to read efficacy limitations into the preamble should be rejected. First, the "method for treating an angiogenic eye disorder" phrase has no bearing on the dosing steps in the claim, 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. (Ex.1001, 13:15-34 (Table 1) (showing that almost 5% of the patients in the 2Q8 arm failed to maintain vision)). In other words, the preamble is merely a statement of *intended* purpose, and therefore, not a limitation. *Bristol-Myers*, 246 F.3d at 1375; *Copaxone*, 906 F.3d at 1022-23.