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.: IPR2023-00533

U.S. Patent No. 10,888,601 B2
Filed: April 29, 2019
Issued: January 12, 2021
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. 10,888,601 B2

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

RULES

MISCELLANEOUS

EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 10,888,601 B2 ("'601 patent")
1002	Expert Declaration of Dr. Thomas A. Albini in Support of Petition for *Inter Partes* Review of Patent No. 10,888,601 B2, dated June 30, 2022 ("Albini")
1003	Expert Declaration of Mary Gerritsen, Ph.D. in Support of Petition for *Inter Partes* Review of U.S. Patent No. 10,888,601 B2, dated June 30, 2022 ("Gerritsen")
1004	Jocelyn Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 PROC. NAT'L ACAD. SCI. 11393 (2002) ("Holash")
1005	Quan Dong Nguyen et al., *A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration*, 116 OPHTHALMOLOGY 2141 (2009) ("Nguyen-2009")
1006	James A Dixon et al., *VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration*, 18 EXPERT OPINION ON INVESTIGATIONAL DRUGS 1573 (2009) ("Dixon")
1007	Adis R&D Profile, *Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye*, 9 DRUGS R&D 261 (2008) ("Adis")
1008	U.S. Patent No. 7,531,173 B2 ("'173 patent")
1009	U.S. Patent No. 7,396,664 B2 ("'664 patent")
1010	U.S. Patent No. 7,374,758 B2 ("'758 patent")
1011	F Semeraro et al., *Aflibercept in Wet AMD: Specific Role and Optimal Use*, 7 DRUG DESIGN, DEV. & THERAPY 711 (2013) ("Semeraro")
1012	Press Release, Regeneron, Regeneron and Bayer 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)")

Exhibit	Description
1013	Press Release, Regeneron, Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration (May 8, 2008), http://investor.regeneron.com/releasedetail.cfm?ReleaseID=394065 ("Regeneron (8-May-2008)")
1014	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW1), NCT00509795, ClinicalTrials.gov (Apr. 28, 2009), https://clinicaltrials.gov/ct2/show/NCT00509795 ("NCT-795")
1015	VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2), NCT00637377, ClinicalTrials.gov (Mar. 17, 2008), https://clinicaltrials.gov/ct2/show/NCT00637377 ("NCT-377")
1016	IPR2021-00881 Ex.1109, Diana V. Do Deposition Transcript (April 21, 2022) ("IPR2021-00881 Ex.1109")
1017	File History of U.S. Patent No. 10,888,601 B2 ("'601 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")

Exhibit	Description
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 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")

Exhibit	Description
1037	CENTER FOR DRUG EVALUATION & RESEARCH, BLA No. 125156, Lucentis Medical Review ("Lucentis MR")
1038	Curriculum Vitae of Dr. Thomas Albini ("Albini CV")
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")
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")

Exhibit	Description
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 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)")

Exhibit	Description
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. AM. 57 (2008) ("Mueller")
1061	Curriculum Vitae of Dr. Mary Gerritsen ("Gerritsen CV")
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)")

Exhibit	Description
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")
1072	Janice M. Reichert, *Antibody-Based Therapeutics To Watch In 2011*, 3 MABS 76 (2011) ("Reichert")
1073	Owen A. Anderson et al., *Delivery of Anti-Angiogenic Molecular Therapies for Retinal Disease*, 15 DRUG DISCOVERY TODAY 272 (2010) ("Anderson")
1074	Thomas A. Ciulla & Philip J. Rosenfeld, *Antivascular Endothelial Growth Factor Therapy For Neovascular Age-Related Macular Degeneration*, 20 CURRENT OPINION OPHTHALMOLOGY 158 (2009) ("Ciulla")
1075	Zhang Ni & Peng Hui, *Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration*, 223 OPHTHALMOLOGICA 401 (2009) ("Ni")
1076	Marco A. Zarbin & Philip J. Rosenfeld, *Pathway-Based Therapies for Age-Related Macular Degeneration: An Integrated Survey of Emerging Treatment Alternatives*, 30 RETINA 1350 (2010) ("Zarbin")
1077	Corporate Finance Institute, *SEC Filings: Public Disclosures About Public Companies*, https://corporatefinanceinstitute.com/resources/data/public-filings/sec-filings/ (last visited May 5, 2021) ("Corporate Finance Institute")
1078	Carl W. Schneider, *Nits, Grits, and Soft Information in SEC Filings*, 121 U. PA. L. REV. 254 (1972) ("Schneider")

Exhibit	Description
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 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")
1086	IPR2021-00881 Ex.2098, CDER, Statistical Review for Application Number 125387 (Nov. 18, 2011) ("IPR2021-00881 Ex.2098")
1087	Amino acid sequence alignment of SEQ ID NO:2 of the '681 and '601 patents with aflibercept amino acid sequence from WHO 2006, SEQ ID NO:16 of the '758 patent, and SEQ ID NO:16 of the '959 patent ("AA Alignment vs 758 and 959 patents")
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

Exhibit	Description
	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., CLINCAL DEVELOPMENT OF VEGF TRAP, *IN* ANGIOGENESIS (William D. Figg & Judah Folkman eds. 2008) ("Rudge-2008")
1092	Amino acid sequence alignment of SEQ ID NO:2 of the '681 and '601 patents with SEQ ID NO:16 of the '758 patent and SEQ ID NO:2 of the '173 patent ("AA Alignment vs 758 and 173 patents")
1093	Nucleotide sequence alignment of SEQ ID NO:1 of the '681 and '601 patents with SEQ ID NO:15 of the '758 patent and SEQ ID NO:1 of the '173 patent ("NA Alignment vs 758 and 173 patents")
1094	ClinicalTrials.gov, *1997: Congress Passes Law (FDAMA) Requiring Trial Registration*, U.S. NAT'L LIBRARY MED. (Oct. 2020), https://clinicaltrials.gov/ct2/about-site/history ("History-ClinicalTrials.gov")
1095	Affidavit of Duncan Hill (Internet Archive Records Request Processor) Regarding 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) and VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2), NCT00637377, ClinicalTrials.gov (Mar. 17, 2008), dated January 27, 2021 ("Wayback-Affidavit-601")
1096	File History of U.S. Patent No. 10,130,681 B2 ("'681 FH")

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 1-9, 34-39, 41-43, and 45 (the "Challenged Claims") of U.S. Patent No. 10,888,601 ("'601 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 published and known to persons of ordinary skill in the art (hereafter, "POSAs") before 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 regimens to POSAs as early as 2008. The dependent claims drawn to visual acuity measures and exclusion criteria either fail to carry patentable weight or are inherent and obvious variations on the subject matter of the independent claims. Accordingly, the Challenged Claims are 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 & Obviousness. Each Challenged Claim is anticipated. VEGF Trap-Eye (aflibercept) and its domain components were known and disclosed in the prior art, including in each of Petitioner's asserted references. (*See* Ex.1006, 1576 (Fig. 1); Ex.1008; Ex.1010).

Petitioner's references disclosing Regeneron's Phase 3 VIEW AMD trials describe all dosing steps of the Challenged Claims—including administering three monthly loading doses of VEGF Trap-Eye/aflibercept, followed by every-8-week dosing. The recited visual acuity measures are unpatentable given that the prior art discloses administration of the same compound according to the same dosing schedule set forth in the claims, and though the recited exclusion criteria are not entitled to patentable weight, they are nonetheless inherent.

The claimed methods also are obvious in view of the risks and financial burden of monthly intravitreal injections—the approved AMD dosing regimen for the existing anti-VEGF therapy prior to EYLEA's approval, LUCENTIS® (ranibizumab). (Ex.1006, 1574). POSAs were motivated to pursue less frequent dosing schedules, like the VIEW Phase 3 clinical trial every-8-week dosing Regeneron itself (among others) placed into the public domain. Combined with the

abundance of positive, prior art data from Regeneron's other clinical trials, a POSA would have reasonably expected success administering the claimed dosing regimens. The recited visual acuity measures do not save the dependent claims from obviousness given that Regeneron's aflibercept molecule already had "Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Ex. 1006, 1573).

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 '601 patent is currently being challenged in *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226 (P.T.A.B.), instituted on January 11, 2023. The instant petition is concurrently filed with *Celltrion, Inc. v. Regeneron Pharms.*, *Inc.*, IPR2022-00532 (P.T.A.B.), challenging U.S. Patent No. 10,130,681 ("'681 patent"). The '681 patent is currently being challenged in *Mylan Pharms. Inc.*

v. Regeneron Pharms., Inc., IPR2022-01225 (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 '601 patent. U.S. Patent Nos. 9,669,069 and 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 joinder 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; 10,130,681 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 claim the benefit of the '601 patent's purported priority date.

C. Lead and Back-Up Counsel and Service Information (37 C.F.R. § 42.8(b)(3)-(4)).

Lead Counsel: Lora M. Green (Reg. No. 43,541)

Back-Up Counsel: Yahn-Lin Chu (Reg. No. 75,946)

Robert Cerwinski (to be admitted pro hac vice)

Aviv Zalcenstein (to be admitted pro hac vice)

Brigid Morris (to be admitted pro hac vice)

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;

ychu@wsgr.com;

rcerwinski@geminilaw.com;

azalcenstein@geminilaw.com;

bmorris@geminilaw.com.

Post: Gemini Law LLP

40 W 24th Street, Suite 6N

New York, NY 10010

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 '601 patent—which issued on November 20, 2018—is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging any claim thereof on the grounds identified herein. Neither Petitioner nor any other RPI has filed a civil action challenging the validity, or been served with a complaint alleging infringement, of the '601 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 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 '601 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), (b) and (d)**. Petitioner submits that neither "the same [nor] substantially the same" art or arguments were previously presented to the Office during prosecution of the Challenged Claims. First, none of Petitioner's grounds rely on prior art actually applied against the claims during prosecution, nor discussed by the Examiner. Instead of the VIEW dosing regimen prior art Petitioner asserts here under §§102 and 103, the Examiner only rejected the claims for obviousness-type double patenting ("OTDP") during prosecution. (Ex.1017, 796-803).

Second, the only fact PO can point to is that Petitioner's asserted references were included among hundreds of references in a series of IDS submissions. 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) (citing *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, Paper 8,

40 (P.T.A.B. Nov. 7, 2018)); *see also Amazon.com, Inc. v. M2M Sols. LLC*, IPR2019-01205, 2020 WL 448385, at *7 (P.T.A.B. Jan. 27, 2020) (instituting IPR where "the prosecution history record shows that the various IDSs include at least about a few hundred references" and "[n]othing in the record indicate[d] that the Examiner substantively considered...the prior art"); *id.* at *7 ("[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." (citations omitted)); *Shenzhen Zhiyi Tech. Co. v. iRobot Corp.*, IPR2017-02137, Paper 9, 9-10 (P.T.A.B. Apr. 2, 2018) (declining to deny institution under §325(d) when reference merely cited in an IDS; reference not relied upon by the Examiner, but rather, was merely "included in the approximately fifteen pages of cited references"); *Nitto Denko Corp. v. Hutchinson Tech. Inc.*, IPR2018-00955, Paper 7, 15-17 (P.T.A.B. Dec. 4, 2018) (instituting IPR review despite asserted reference being submitted in an IDS which the examiner initialed). Indeed, PO's serial IDS submissions of Petitioner's asserted art buried among hundreds of other references does not rise to the level of candor and good faith required before the Patent Office.

In short, Petitioner's asserted prior art references were neither "involved" nor "evaluated" during prosecution, and therefore, the art and arguments provided herein

are neither the same nor substantially the same as those previously considered by the Office.[1] *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. §325(d).

***Becton, Dickinson* Factors (c), (e), (f): The Examiner Erred**. As explained above, the intrinsic record does not reflect that Petitioner's grounds were presented to, or considered by, the Examiner. Nonetheless, to the extent the Board disagrees and determines *Becton Dickinson* factors (a), (b), and (d) are satisfied, discretionary denial still is unwarranted because the Examiner overlooked each reference's anticipatory disclosures, constituting material error, relying instead on a single round of OTDP rejections over patents in the same family.[2] *See Advanced Bionics*, 2020 WL 740292, at *4 (listing silence as evidence of error). As shown below, multiple

[1] Should PO point to its 2018 and 2019 IDS submissions including Dixon and a corresponding claim chart during prosecution of the related '345 patent, that disclosure is only directed to quarterly and PRN dosing claims—not the 8-week dosing—and thus is irrelevant to the Challenged Claims.

[2] Indeed, the Examiner assigned to this family has fallen into a pattern of only asserting OTDP rejections against most pending claims, consistently ignoring relevant art and the claims' significant § 112 issues, leading Regeneron to obtain a thicket of dosing regimen patents. No fewer than seven (7) patents already have issued from this family, and five (5) applications remain pending

prior art references disclose the VIEW 8-week dosing regimen and clearly anticipate the issued claims; the only plausible explanation for the Examiner not rejecting the claims based on those disclosures is failure to have seen, appreciated or understood the disclosures.

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, including, *inter alia*, the dependent claims' best corrected visual acuity ("BCVA") limitations, and the additional art and asserted combinations relevant to the exclusion criteria. *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 (P.T.A.B. Dec. 9, 2013) (same).

In sum, Petitioner presents challenges never applied or considered by the Examiner during prosecution of the '601 patent claims, and the Examiner's failure to reject claims over the art and grounds herein constitutes material error.

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

A. STATUTORY GROUNDS OF CHALLENGE.

The following prior art references anticipate the Challenged Claims:

Ground	Proposed Rejections Under 35 U.S.C. § 102
1	Dixon
2	Adis
3	Regeneron (8-May-2008)
4	NCT-795

In addition, the following render the Challenged Claims obvious:

Ground	Proposed Rejections Under 35 U.S.C. § 103
5	Dixon alone or in view of the '758 or '173 patents
6	Dixon in combination with Rosenfeld-2006 (and if necessary, the '758 or '173 patents) (claims 9 and 36)
7	Dixon in combination with Heimann-2007 (and if necessary, the '758 or '173 patents) (claims 9 and 36)

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 '601 PATENT.[3]

The '601 patent confirms that angiogenic eye disorders, such as AMD, were known to be effectively treated through vascular endothelial growth factor ("VEGF")[4] inhibition. (Ex.1001, 1:31-60). Indeed, prior to 2011, ranibizumab (LUCENTIS®), an anti-VEGF antibody fragment marketed by Genentech, was FDA-approved for monthly administration via intravitreal injection to treat AMD. (*Id.*, 1:57-60; *see also* Ex.1048, 1). Despite being approved for monthly dosing, ranibizumab was often administered on a PRN (*i.e.*, *pro re nata*, or "as needed") basis, and Genentech's clinical trials were testing extended dosing regimens, and showing that PRN dosing could achieve similar outcomes to monthly dosing, using fewer injections. (Ex.1030, 6-7; Ex. 1002, ¶¶72-74). Bevacizumab (AVASTIN®),

---

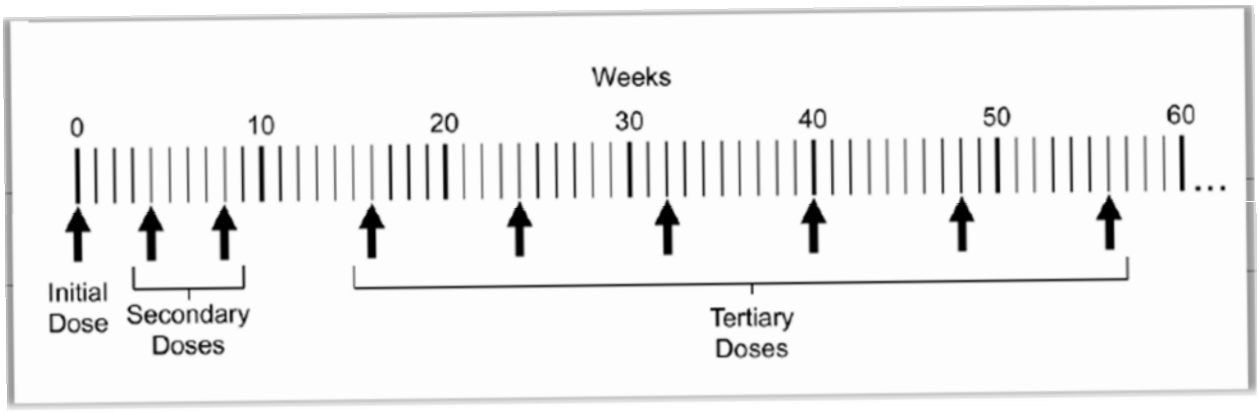
[3] Solely for this IPR, Petitioner assumes a January 13, 2011 priority date, but reserves all rights to challenge said priority date. The '601 patent is subject to the AIA given the inclusion of new matter in Application No. 13/940,370, filed July 12, 2013.

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

an anti-VEGF antibody, was not approved for ocular indications, but was extensively used off-label to treat angiogenic eye disorders. (Ex.1006, 1574; Ex. 1002, ¶64). Because there was no approved dosing regimen for bevacizumab in treating eye disorders, it too was often administered PRN. (Ex.1025, 1369; Ex. 1047, 8; Ex. 1049, 24-25; Ex. 1002, ¶73). In other words, extended dosing regimens were already in use prior to 2011. Yet the '601 patent purports a need in the art for regimens that allow less frequent dosing. (Ex.1001, 1:64-67).

The '601 patent broadly claims the prior art VIEW1/VIEW2 regimen, which became the FDA-approved regimen for EYLEA® (i.e., VEGF Trap-Eye/aflibercept). (*See, e.g.*, Ex.1001, 21:41-46 (Claim 1)). Dependent claims include efficacy criteria wherein the subject of the claimed method loses less than, or gains at least, fifteen letters of Best Corrected Visual Acuity (BCVA) score. (*See, e.g.*, *id.*, 21:49-51 (Claim 3); *id.*, 21:55-56 (Claim 5)). The '601 patent claims also include variations of two of the thirty-seven exclusion criteria for the prior art VIEW1/VIEW2 trials: "18. Active intraocular inflammation in either eye. 19. Active ocular or periocular infection in either eye," while omitting the other thirty-five exclusion criteria. (*Id.*, 11:44-45; *id.*, 21:65-67 (Claim 9); *id.*, 24:22-24 (Claim 36); *see id.*, 10:64 – 12:22). The exclusion criteria are mentioned only once in the specification, in Example 4, describing the Phase 3 AMD VIEW trials. (*See id.*, 9:21 – 14:4).

This VIEW1/VIEW2 dosing regimen is described as "an exemplary dosing regimen of the present invention" and is depicted graphically by the Figure of the '601 patent:



(*Id.*, 2:55-62, Fig.1; *see also id.*, 4:10-12). The Figure illustrates and exemplifies a dosing regimen falling within the Challenged Claims.

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

Under 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.