UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Inter Partes Review No.: IPR2022-01524

U.S. Patent No. 11,253,572
Filed: June 21, 2021
Issued: February 22, 2022
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. 11,253,572

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EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 11,253,572 ("'572 patent")
1002	Declaration of Angelo P. Tanna, M.D.
1003	Curriculum Vitae of Angelo P. Tanna, M.D.
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	F. Semeraro et al., *Aflibercept in Wet AMD: Specific Role and Optimal Use*, 7 DRUG DESIGN, DEV. & THERAPY 711 (2013) ("Semeraro")
1009	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)")
1010	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")

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1011	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")
1012	U.S. Patent Nos. 7,303,746 B2; 7,303,747 B2; 7,306,799 B2; and 7,521,049 B2 ("Monthly-Dosing-Patents")
1013	File History of U.S. Patent No. 9,254,338 B2 ("'338 FH")
1014	Jeffrey S. Heier et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration*, 119 OPHTHALMOLOGY 2537 (2012) ("Heier-2012")
1015	Jeffrey S. Heier, *Intravitreal VEGF Trap for AMD: An Update*, RETINA TODAY, Oct. 2009, 44 ("Heier-2009")
1016	Regeneron Pharm., Inc., Quarterly Report (Form 10-Q) (Sept. 30, 2009) ("2009 10-Q")
1017	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)")
1018	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")
1019	LUCENTIS® Prescribing Information (2006) ("Lucentis")
1020	Janice M. Reichert, *Antibody-Based Therapeutics To Watch In 2011*, 3 MABS 76 (2011) ("Reichert")
1021	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")
1022	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,

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	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-038")
1023	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")
1024	Expert Declaration of David M. Brown, M.D., submitted in IPR2021-00881 as Patent Owner Exhibit 2050 on February 11, 2022.
1025	Hecht, "Opthalmic Preparations," Remington: The Science and Practice of Pharmacy, Volume II, 19th edition, Chapter 89 (1995).
1026	Rosenfeld et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31; supplemental appendix ("Rosenfeld")
1027	Randolph and Jones, "Surfactant-Protein Interactions," Rational Design of Stable Protein Formulations, edited by Carpenter and Manning, vol. 13, 2002 ("Randolph")
1028	Fraser et al., Journal of Clinical Endocrinology and Metabolism, February 2005, 90(2):1114–1122 ("Fraser")
1029	Saishin et al., "VEGF-TRAP$_{R1R2}$ Suppresses Choroidal Neovascularization and VEGF-Induced Breakdown of the Blood-Retinal Barrier," Journal of Cellular Physiology, 195:241-248 (2003) ("Saishin").
1030	Appendix to Heier et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration*, 119 OPHTHALMOLOGY 2537 (2012) ("Heier-2012 Appendix")
1031	FDA, Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry (Nov. 2016).
1032	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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1033	Rama D. Jager, *Risks of Intravitreous Injection: A Comprehensive Review*, 24 J. RETINAL & VITREOUS DISEASE 676 (2004) ("Jager-2004")
1034	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")
1035	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")
1036	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)")
1037	Napoleone Ferrara & Robert S. Kerbel, *Angiogenesis as a Therapeutic Target*, 438 NATURE 967 (2005) ("Ferrara-2005")
1038	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")
1039	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Central Retinal Vein Occlusion (CRVO), NCT01012973, ClinicalTrials.gov (Nov. 12, 2009), https://clinicaltrials.gov/ct2/show/NCT01012973 ("NCT-973")
1040	*Reserved*
1041	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-

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	details/positive-interim-phase-2-data-reported-vegf-trap-eye-age-related?releaseid=394105 ("Regeneron (27-March-2007)")
1042	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)")
1043	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)")
1044	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)")
1045	Press Release, Regeneron, Bayer and Regeneron Extend Development Program for VEGF Trap-Eye to Include Central Retinal Vein Occlusion (Apr. 30, 2009), https://investor.regeneron.com/news-releases/news-release-details/bayer-and-regeneron-extend-development-program-vegf-trap-eye ("Regeneron (30-April-2009)")
1046	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)")
1047	Press Release, Regeneron, VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients with Diabetic Macular Edema (Feb. 18, 2010), https://investor.regeneron.com/news-releases/news-release-

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	details/vegf-trap-eye-shows-positive-results-phase-2-study-patients?releaseid=445521 ("Regeneron (18-February-2010)")
1048	Press Release, Bayer, Bayer HealthCare and Regeneron 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) ("Bayer (19-August-2008)")
1049	Campochiaro et al., *Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusions: two-year outcomes*, Ophthalmology, 117 (2010), pp. 2387-2394. ("Campochiaro")
1050	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")
1051	Owen A. Anderson et al., *Delivery of Anti-Angiogenic Molecular Therapies for Retinal Disease*, 15 DRUG DISCOVERY TODAY 272 (2010) ("Anderson")
1052	Thomas A. Ciulla & Philip J. Rosenfeld, *Antivascular Endothelial Growth Factor Therapy For Neovascular Age-Related Macular Degeneration*, 20 CURRENT OPINION OPHTHALMOLOGY 158 (2009) ("Ciulla")
1053	Zhang Ni & Peng Hui, *Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration*, 223 OPHTHALMOLOGICA 401 (2009) ("Ni")
1054	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")
1055	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")
1056	Carl W. Schneider, *Nits, Grits, and Soft Information in SEC Filings*, 121 U. PA. L. REV. 254 (1972) ("Schneider")

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1057	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")
1058	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")

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Apotex Inc. ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. §§ 42 *et seq.*, seeking cancellation of claims 1-14 and 26-30 (the "Challenged Claims") of U.S. Patent No. 11,253,572 ("'572 patent") (Ex.1001), assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

I. INTRODUCTION

The Challenged Claims are directed to a method of treating a known indication with a known dosage regimen of a known active ingredient. Long before the patent's alleged 2011 priority date, Regeneron had disclosed that it's age-related macular degeneration ("AMD") clinical trials (VIEW1/VIEW2) with EYLEA® (aflibercept) were designed to use the precise dosing regimen now covered by the Challenged Claims. Regeneron publicly disclosed the exact dosing regimen as early as 2008, three years prior to filing its patent application. While Regeneron added certain efficacy endpoints that result upon administering the claimed dosage regimen, such claim elements are not given patentable weight. But even if they were, the prior art nevertheless anticipates the Challenged Claims.

The caselaw is clear here. It is not patentable to merely observe the efficacy of administering a known compound using a known method to treat a known condition. *See, e.g., In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2013); *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010); *In re*

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Omeprazole Patent Litig., 483 F.3d 1364, 1373 (Fed. Cir. 2007); *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005); *Bristol–Myers Squibb Co. v. Boehringer Ingelheim Corp.*, 86 F. Supp. 2d 433, 443 (D.N.J. 2000), *aff'd in relevant part*, 246 F.3d 1368 (Fed. Cir. 2001). Simply put, the Challenged Claims are not patentable.

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

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

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

Petitioner Apotex Inc. is the real party-in-interest. Additional real parties-in-interest are Apotex Corp., Apotex Pharmaceutical Holdings Inc. and Aposherm Delaware Holdings Corp.

No other parties exercised or could have exercised control over this Petition; no other parties funded, directed and controlled this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48759- 60 (Aug. 14, 2021).

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

Petitioner identifies the following IPR proceedings that are currently pending on patents related to the ’572 patent:

- Challenging U.S. Patent No. 9,254,338 (the ‘338 patent):

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- *Mylan Pharms. Inc. v. Regeneron Pharms. Inc.*, No. IPR2021-00881 (P.T.A.B.), filed May 5, 2021,
- *Celltrion Inc. v. Regeneron Pharms, Inc.*, No. IPR2022-00258 (P.T.A.B.), filed December 9, 2021, and
- *Apotex Inc. v. Regeneron Pharms, Inc.*, No. IPR2022-00298 (P.T.A.B.), filed December 9, 2021.

- Challenging U.S. Patent No. 9,669,069:
  - *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00880 (P.T.A.B.), filed May 5, 2021,
  - *Celltrion Inc. v. Regeneron Pharms, Inc.*, No. IPR2022-00257 (P.T.A.B.), filed December 9, 2021, and
  - *Apotex Inc. v. Regeneron Pharms, Inc.*, No. IPR2022-00301 (P.T.A.B.), filed December 9, 2021.
- Challenging U.S. Patent No. 10,130,681:
  - *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01225 (P.T.A.B.), filed July 1, 2022.
- Challenging U.S. Patent No. 10,888,601:

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- *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2022-01226 (P.T.A.B.), filed July 1, 2022.

Petitioner identifies the following district court proceeding that is currently pending and involves the '572 patent as well as related patents: *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.,* No. 1:22-cv-00061-TSK (N.D. W.Va).

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

U.S. Patent Nos. 9,254,338; 9,669,069; 10,130,681; 10,857,205; 10,828,345; and 10,888,601; and U.S. Patent Application Nos. 17/072,417; 17/112,404; 17/112,063; and 17/350,958 are all related to the '572 patent.

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

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

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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 No. 05-1323 (Customer ID No. 23911).

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

Petitioner certifies that the '572 patent—which issued on February 22, 2022—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 real party-in-interest has filed a civil action challenging the

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validity, or been served with a complaint alleging infringement, of the '572 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. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION TO DENY INSTITUTION

The Board should not exercise its discretion to deny institution based on the mere citation by the Applicant of certain references used in this Petition in Information Disclosure Statements ("IDS"). The examiner's failure to address any of the references used in this Petition on the merits favors institution.

To apply §325(d), the Board uses the following two-part framework: "(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims." *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020). "An example of material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Id*. at 8 n.9. In applying this two-part framework, the Board has identified several nonexclusive factors that may be considered ("the

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Becton factors"). *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017). Factors (a), (b), and (d) correspond to the first part of the framework, and factors (c), (e), and (f) fall within part two of the framework. *Advanced Bionics*, at 8-10.

Dixon, Regeneron (8-May-2008), NCT-795, and NCT-377, used in this Petition as anticipatory references, are merely a few of the hundreds of references submitted to the Patent Office in various Information Disclosure Statements during the very short prosecution. Although the examiner acknowledged the IDSs, there is no evidence that he substantively considered the references relied upon herein. In fact, the Examiner did not present any rejections based on prior art in the *one and only* Office Action, instead only presenting double patenting rejections over several patents in the same family.

The 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 Pharm.*, Inc., IPR2019-00740, Paper 15 at 65 (PTAB Aug. 30, 2019); *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, slip op. at 40 (PTAB Nov. 7, 2018) (Paper 8) (declining to deny institution based on § 325(d) where reference was listed on the face of the patent, but patent owner provided no evidence "about the extent to which the [e]xaminer evaluated" the reference during prosecution); *Digital*

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Check Corp. d/b/a ST Imaging v. E-Imagedata Corp., IPR2017-00178, slip op. at 12-13 (PTAB Apr. 25, 2017) (Paper 6) (granting institution even though a prior art reference was cited in an IDS because there was no indication that the claims were substantively discussed by the examiner during prosecution); *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, slip op. at 7-9 (PTAB Apr. 3, 2017) (Paper 8) (refusing to deny institution based on § 325(d) when a prior art reference was cited in an IDS but was not considered by the examiner at any length). This pattern is particularly consistent where, as here, a relevant reference is merely cited in an IDS but not applied by the Examiner in making a rejection. See *Apotex, Inc. v. UCB Biopharma, SPRL*, IPR2019-00400, Paper 17 at 24-25 (PTAB July 15, 2019).

Petitioner does not contend that Dixon, Regeneron (8-May-2008), NCT-795, and NCT-377 were not presented to the Office. Thus, the relevant analysis here relates to part two of the *Advanced Bionics* framework. Part two of the *Advanced Bionics* framework considers whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, at 8. As *Advanced Bionics* explains, considering *Becton* factors (c), (e), and (f) can provide guidance as to whether the Office erred. *Roku, Inc. v. Universal Elecs., Inc.*, IPR2019-01619, Paper 11 at 12 (PTAB Apr. 2, 2020). As explained below, each of these factors demonstrate the material error by the Office.

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Regarding factor (c), there is no evidence that Dixon, Regeneron (8-May-2008), NCT-795, or NCT-377 were evaluated at all during examination, and it is indisputable that they were never the basis for a rejection. There is no discussion of any of these references in the one Office Action in the '572 patent's prosecution history. This factor therefore weighs strongly against exercising § 325(d) discretion. *See Hyperbranch Med. Tech., Inc. v. Confluent Surgical, Inc.*, IPR2018-01097, Paper 14 at 24 (PTAB Nov. 14, 2018) (Prior art "simply being of record, but not applied in any rejection by the Examiner during examination…, provides little impetus for [the Board] to exercise [its] discretion to deny institution under § 325(d)"); *Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp.*, IPR2020-00040, Paper 21 at 18 (PTAB May 12, 2020) (finding material error where "[t]he Examiner never discussed [asserted prior art cited in IDS] or made a rejection based on it").

Regarding factors (e) and (f), as demonstrated herein, the asserted references anticipate all but four of the Challenged Claims, and these references, in combination with a reference that was <u>not</u> before the Office during prosecution (Hecht) renders obvious the remaining Challenged Claims. Thus, Petitioner has demonstrated that the Examiner's failure to consider Dixon, Regeneron (8-May-2008), NCT-795, or NCT-377 and the disclosures relied on in this Petition constitutes material error. The *Amgen* case cited above is highly instructive in this regard. The Board held that the failure of the examiner to apply prior art that served as the primary reference in an

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IPR can itself constitute material error. *Amgen*, IPR2019-00740, Paper 15 at 65. And, in arriving at that holding, the Board credited five other proceedings where the Board declined to exercise its discretion under § 325(d) when a reference was previously disclosed, but never substantively considered by the Examiner. *Amneal Pharms.,* IPR2018-00943, Paper 8 at 40; *Digital Check*, IPR2017-00178, Paper 6 at 12–13; *Fox Factory*, IPR2016-01876, Paper 8 at 7–9; *HyperBranch Med. Tech.,* IPR2018-01097, Paper 14 at 17; *Praxair Distrib., Inc. v. INO Therapeutics LLC*, No. IPR2015-00893, Paper 14 at 8 (PTAB Sept. 22, 2015).

Furthermore, the Board has consistently held that under these circumstances, the question of whether an Examiner materially erred under *Becton* factor (e) cannot be answered without evaluating whether the prior art challenge presented in the Petition demonstrates a likelihood of success on the merits. These cases find material error consistent with factor (e) when such a likelihood has been demonstrated. *See e.g, Skechers U.S.A., Inc. v. Nike, Inc*., Paper 10 at 19-20 (PTAB May 19, 2021) (petitioner demonstrated material error by demonstrating a "reasonable likelihood of prevailing" in its anticipation argument regarding a reference cited in an IDS but not substantively considered by the Examiner); *HTC Corp. v. Motiva Patents, LLC*, IPR2019-01666, Paper 9 at 10 (PTAB Apr. 3, 2020) (petitioner demonstrated a material error under the second part of the *Advanced Bionics* framework when two references cited in an IDS but not substantively considered by the Examiner during

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prosecution disclosed all the limitations of the claims). The Board has already preliminarily evaluated whether Dixon, Regeneron (8-May-2008), NCT-795, and NCT-377 teach the dosage regimen claimed in the '572 patent (as it's the same dosage regimen claimed in the '338 patent), and found in the affirmative. *See* IPR2021-00881, Paper 21, Institution Decision at 28, 32 (November 10, 2021) (granting institution on claims covering the same dosage regimen based on grounds using the same prior art).

Accordingly, in view of the material error by the Examiner, the Board should not exercise its discretion to deny institution.

VI. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

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

VII. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

A. CHALLENGED CLAIMS

Petitioner requests IPR of claims 1-14 and 26-30 of the '572 patent, and cancellation of these claims as unpatentable.

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B. STATUTORY GROUNDS OF CHALLENGE

Each of the following prior art references anticipate claims 1-5, 8-11, 14, and 26-30:

Ground	Claims	Proposed Rejections Under 35 U.S.C. § 102
1	1-5, 8-11, 14, and 26-30	Dixon
2	1-5, 8-11, 14, and 26-30	Regeneron (8-May-2008)
3	1-5, 8-11, 14, and 26-30	NCT-795
4	1-5, 8-11, 14, and 26-30	NCT-377

In addition, at least the following render the claims 6, 7, 12, and 13 obvious:

Ground	Claims	Proposed Rejections Under 35 U.S.C. § 103
5	6, 7, 12, and 13	Dixon or Regeneron (8-May-2008) or NCT-795 or NCT-377 in view of Hecht

Petitioner's full statement of reasons for the relief requested is set forth in greater detail below, and in the supporting Expert Declaration of Dr. Angelo Tanna (Ex.1002).

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VIII. OVERVIEW OF THE '572 PATENT

A. THE '572 PATENT[1]

The '572 patent teaches that angiogenic eye disorders, such as AMD, and diabetic macular edema ("DME"), were known to be effectively treated through vascular endothelial growth factor ("VEGF")[2] inhibition. Ex.1001, 1:40-65. Indeed, prior to the '572 patent priority date, ranibizumab (LUCENTIS®), an anti-VEGF antibody fragment marketed by Genentech, was FDA-approved for monthly administration via intravitreal injection to treat angiogenic eye disorders, including AMD. *Id.*, 1:65-2:2; Ex.1019, 1.

The '572 patent claims dosing regimens for treating angiogenic eye disorders, including AMD, via the known method of: (1) administering a single initial dose of 2 mg of aflibercept, followed by (2) one or more "secondary doses" of 2 mg of

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[1] Solely for purposes of this IPR, Petitioner assumes a January 13, 2011 priority date. However, Petitioner reserves all rights to challenge the extent to which Regeneron asserts application of pre-AIA standards of patentability.

[2] Vascular endothelial growth factor (VEGF) is a "naturally occurring glycoprotein in the body that acts as a growth factor for endothelial cells." Ex.1008, 711; Ex.1002, ¶44. Early research linked activity of VEGF-A to the development of ocular diseases such as neovascular AMD. Ex.1018, 627-28; Ex.1002, ¶¶44-48.

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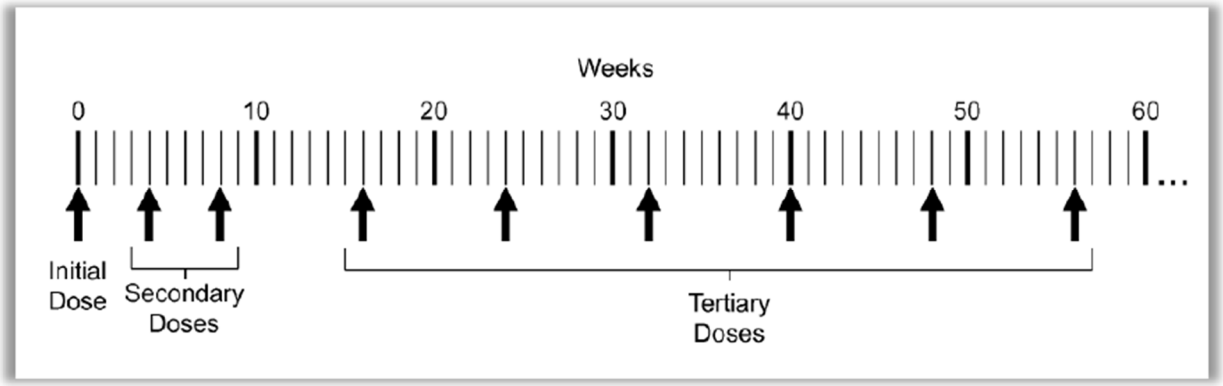
aflibercept administered approximately four weeks after the immediately preceding dose, followed (3) by one or more "tertiary doses" of 2 mg of aflibercept administered approximately eight weeks following the immediately preceding dose. (*e.g., id.*, Claim 1). The '572 patent also specifically claims the prior art VIEW1/VIEW2 regimen, which eventually became the FDA-approved regimen for EYLEA® (i.e., VEGF Trap-Eye/aflibercept):

> [A] single initial dose of a VEGF antagonist is administered to a patient on the first day of the treatment regimen (i.e., at week 0), followed by two secondary doses, each administered four weeks after the immediately preceding dose (i.e., at week 4 and at week 8), followed by at least 5 tertiary doses, each administered eight weeks after the immediately preceding dose (i.e., at weeks 16, 24, 32, 40 and 48).

Id., 4:10-17, 2:61-67, claims 5 and 27. This VIEW1/VIEW2 dosing regimen is described as "an exemplary dosing regimen of the present invention" and is depicted graphically by Figure 1 of the '572 patent:



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Id., (Fig.1), 4:10-21.

During prosecution of a parent application filed early in the priority chain (now U.S. Patent No. 9,254,338), Regeneron told the Examiner that Example 5 of the rejected patent application "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 once every 8 weeks) for the effective treatment of diabetic macular edema (DME)." Ex.1013, 9/11/2015 Response, 8. One Example 5 dosing regimen is identical to the VIEW1/VIEW2 regimen for AMD that was publicly disclosed years before the '572 patent filing.

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). Under *Phillips*, claim terms are typically given their ordinary and customary meanings, as would have been understood by a POSA, at the time of the invention, taking into consideration the language of the claims, the specification, and the prosecution history of record. *Phillips*, 415 F.3d at 1313; *also id.*, 1312-16. Petitioner and Dr. Tanna have applied this standard.

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For purposes of this Petition, Petitioner respectfully submits that only the claim terms identified below require further construction.[3]

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

The Challenged Claims recite the phrases "initial dose," "secondary dose," and "tertiary dose." Each is expressly defined in the '572 patent specification:

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

Ex.1001, 3:51-65 (emphasis added); Ex.1002, ¶62.

The specification further explains that "the immediately preceding dose" means "in a sequence of multiple administrations, the dose of VEGF antagonist

[3] Terms need only be construed "to the extent necessary to resolve the controversy." *Vivid Techs., Inc. v. Am. Sci & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *VIZIO, Inc. v. Nichia Corp.*, IPR2017-00558, Paper 9, at 8 (July 7, 2017). Petitioner reserves the right as necessary to address additional limitations in litigation (e.g., for non-infringement) or respond to issues raised by Regeneron.

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which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses." Ex.1001, 4:4-9; Ex.1002, ¶63.

Each claim term should be construed consistent with these express definitions: "initial dose" means "the dose which is administered at the beginning of the treatment regimen"; "secondary dose(s)" means "the dose(s) which are administered after the initial dose"; and "tertiary dose(s)" means "the dose(s) which are administered after the secondary dose(s)." Ex.1002, ¶64.

B. "4 WEEKS" AND "8 WEEKS," AFTER THE IMMEDIATELY PRECEDING DOSE

"4 weeks" A skilled artisan would understand the phrase "4 weeks"—as it appears in the Challenged Claims—to be synonymous with monthly administration. Ex.1002; Ex.1001, 8:9-11; *id.*, 15:19-30; Ex.1002, ¶65.

"8 weeks" A skilled artisan would understand the phrase "8 weeks"—as it appears in the Challenged Claims—to be synonymous with bi- monthly (or every-other-month administration). Ex.1001, 8:9-11, 15:19-30; Ex.1002, ¶66.

C. "WHEREIN THE PATIENT ACHIEVES/GAINS…"

The recitations in the claims stating the intended results of administering aflibercept according to the claimed method do not have patentable weight because they do not alter the steps of the method. Accordingly, these claim elements should not be treated as a limitation on the Challenged Claims.

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Claim 1 states that after administration of aflibercept according to the claimed dosage regimen, "patient achieves a gain in visual acuity within 52 weeks following the initial dose." Dependent claims 2-4 and 8-10 further specify the particular amount of gain and the timing for achieving those gains that the method achieves. Additionally, independent claims 26 and 29 recite that "the method is as effective in achieving a gain in [or maintaining in claim 29] visual acuity as monthly administration of 0.5 mg of ranibizumab…" Dependent claims 28 and 30 further specify the amount of gain or maintenance that the claimed method achieves.

None of the above-described clauses alter or change the steps of the method. Instead these clauses recite the intended result of following the claimed method. Ex.1002, ¶67. Recitations of intended results of a method should not be given patentable weight. *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (holding that the phrase "in a stabilizing amount" recited in the body of the claim was not limiting because it "simply describes the intended result of using the weight to volume ratios recited in the claims"); *Endo Pharm. Inc. v. Watson Labs., Inc.*, No. 2:13-cv-192, 2014 WL 2859349, at *6, *8 (E.D. Tex. Jun. 23, 2014) (holding that the claim term "thereby administering a topically or systemically active agent with increased penetration" recited in the body of the claim was non-limiting because it was "simply a statement of intended result or purpose, to be accorded no weight"); *In re Copaxone*, Civil Action No. 14–1171-GMS, 2016 WL 873062, at *2

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n.1–2 (D. Del. Mar. 7, 2016) (finding language such as "regimen being *sufficient to* alleviate the symptom of the patient" to be non-limiting); *also* Ex.1002, ¶67 (explaining that the statements of intended results do not change or alter the steps of the claimed methods).

In a case with strikingly similar claims and facts to those presented here, the Federal Circuit held that a recitation of an intended result, "reduced hematologic toxicity," was not limiting because the expression "does not result in a manipulative difference in the steps of the claim." *Bristol*, 246 F.3d at 1376. In that case, the claims were drawn to an old (and known) method, treating a patient suffering from a taxol-sensitive tumor with a taxol, and also recited intended results, "reduced hematologic toxicity." As a matter of claim construction, the court held that the expressions of intended results were not limiting: claims with recitations of different intended results are co-extensive and are each limited to practicing the actual steps of the claims, "without regard to the result of performing the claimed steps." *Id*.

The Federal Circuit in that case also rejected an argument that the recitation of intended results must be a limitation so as to preserve the validity of the claims, which differed from the prior art only in the intended results:

> Bristol is correct that new uses of known processes may be patentable ...However, the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by [the prior

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art]. Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.

Id. at 1376.

In this case, the statements of intended results are similarly not limiting, as the expression does not result in a manipulative difference in the steps of the claim. Neither the doctrine of claim differentiation, nor an alleged newly discovered result of a known process, directed to the same purpose as taught by the prior art—to treat angiogenic eye disorders—render these intended results as limitations of the claims.

D. "WHEREIN EXCLUSION CRITERIA FOR THE PATIENT INCLUDE BOTH OF…"

The Challenged Claims recite the following exclusion criteria:

- "active ocular inflammation"
- "active ocular or periocular infection."

Ex.1001, claim 14. For the following reasons, "exclusion criteria" should not be treated as a limitation on the Challenged Claims.

1. The "Exclusion Criteria" are entitled no patentable weight under the printed matter doctrine

Determining whether a claim limitation is entitled to patentable weight under the printed matter doctrine is a two-step process. The first "is the determination that the limitation in question is in fact directed toward printed matter." *In re Distefano*, 808 F.3d 845, 848 (Fed. Cir. 2015). The second "is to ascertain whether the printed

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matter is functionally related to" the rest of the claim. *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018).

In *Praxair Distribution*, the Federal Circuit affirmed the Board's decision to apply the printed matter doctrine and grant no patentable weight to a method claim limitation under which a medical provider would "elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide" in patients with "pre-existing left ventricular dysfunction." *Id.* at 1029. The limitation—deciding not to treat the patient—constitutes a mental step on the basis of information (a pre-existing condition). *Id.* at 1033. Indeed, the mental step of deciding not to treat a patient is unpatentable because "[o]nce the information is detected, no... treatment is given. And as far as the claim specifies, the patient's state may remain unchanged and natural bodily processes may proceed." *INO Therapeutics LLC v. Praxair Distribution Inc.*, 782 F. App'x 1001, 1008 (Fed. Cir. 2019). The facts here are analogous.

The "Exclusion Criteria" Limitation Is Directed Toward Printed Matter. In the '572 patent, the "exclusion criteria" (*i.e.*, preexisting conditions) represent informational content regarding the patient, and therefore, should be considered "printed matter" that are accorded "no patentable weight." Like the "elect[ing]" step in *Praxair Distribution*, no active step of applying (or assessing the patient for) the "exclusion criteria" in the Challenged Claims, is sufficient to impart patentability to

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that mental step/printed material element. Even assuming that application of the "exclusion criteria" could be inferred, the Challenged Claims do not dictate that any step be taken or that any alteration be made to the claimed dosing regimen.

The Printed Matter Is Not Functionally Related To The Rest Of The Claim. There is no functional relationship between the "exclusion criteria" (*i.e.*, preexisting conditions) and the rest of the claim (operative steps of administering a VEGF antagonist to treat an angiogenic eye disorder). Neither the presence nor absence of any "exclusion criteria" dictate any changes to the claimed dosing steps—*i.e.*, the operative steps always remain the same. Ex.1002, ¶68.

Thus, because the "exclusion criteria" are "directed to mental steps" that "attempt to capture informational content," and lack a functional relationship to the other steps of the claimed treatment method, they should be "considered printed matter lacking patentable weight." *Praxair*, 890 F.3d at 1033.

2. The Board should apply the printed matter doctrine as part of its claim construction analyses

To the extent PO argues that whether the "exclusion criteria" are unpatentable mental steps is a determination under 35 U.S.C. § 101, PO is mistaken. The Board's application of the printed matter doctrine to the "exclusion criteria" is an effort to define the scope and meaning of specific claim terms. *In re Gulack*, 703 F.2d 1381, 1385 (Fed. Cir. 1983); *Praxair*, 890 F.3d at 1033.

Here, whether the "exclusion criteria" are directed to informational content without a functional relationship to the other claim limitations "require[s] analyzing and interpreting the meaning of the claim language. ***That is claim construction***, which is ultimately a legal inquiry." *Praxair*, 890 F.3d at 1033 (emphasis added).

X. PERSON OF ORDINARY SKILL IN THE ART

A POSA is presumed to be aware of all pertinent art, think along the lines of conventional wisdom, and possess common sense and ordinary creativity in the pertinent field. A POSA here would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists. Ex.1002, ¶16.

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XI. THE SCOPE AND CONTENT OF THE PRIOR ART

A. TECHNOLOGY BACKGROUND

Aflibercept is an engineered prior art fusion protein consisting of domain 2 of the human VEGF receptor 1 (VEGFR1); domain 3 of the human VEGF receptor 2 (VEGFR2); fused to the Fc portion of human IgG_1. Ex.1004, 11394 (Fig.1A); Ex.1002, ¶49. Aflibercept was developed as an oncology product to treat cancer and as an intravitreal injection to treat angiogenic eye disorders. Ex.1016, Ex.1007; Ex.1002, ¶¶50-51.

The prior art states that aflibercept, VEGF Trap–Regeneron, VEGF Trap-Eye, and VEGF-$Trap_{R1R2}$, among others, are simply different names for the same active ingredient. *E.g.,* Ex.1007; Ex.1006, 1575; Ex.1016, 20; Ex.1005, 2142; Ex.1002, ¶54-55; Ex.1024, p.35, n.30, citing Ex. 1014).

Aflibercept was developed to target angiogenic disorders, including eye disorders, such as AMD, DME, and RVO. Ex.1002, ¶¶50-53. As Dixon states, aflibercept is a VEGF receptor decoy with "high affinity for all VEGF isoforms, binding more tightly than their native receptors." Ex.1006, 1575, 1577.

Earlier generation therapeutics for angiogenic eye disorders that sought to block VEGF included ranibizumab (LUCENTIS®) and bevacizumab (AVASTIN®). Ex.1002, ¶56. Both of these therapies are monoclonal antibodies, which bind to, and inhibit the activity of, VEGF-A. However, the monthly-dosing

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regimen for ranibizumab was costly and inconvenient, leading researchers to: (1) investigate less-frequent dosing regimens, and (2) focus on new drugs with extended duration of action. Ex.1006, 1574; Ex.1002, ¶56. One such drug was another VEGF antagonist, VEGF-Trap$_{R1R2}$ (the active ingredient in EYLEA®) described by Holash in 2002. Ex.1002, ¶56.

Prior to the earliest filing date of the '572 patent, the identity of aflibercept was disclosed in the prior art. *E.g.*, Ex.1007, 261; Ex.1006, 1575; Ex.1002, ¶57. The molecular structure for aflibercept was not only known to the skilled artisan, but would have been an inherent aspect of each of the prior art references that disclose VEGF Trap-Eye/aflibercept. *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380 (Fed. Cir. 2002) ("Under the doctrine of inherency, if [a claim] element is not expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element 'is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'").

Aflibercept was placed into clinical studies in the mid-2000's. Ex.1002, ¶¶54, 58; Ex.1005, 2142, 2147. In 2008, Regeneron publicly announced its Phase 2 trial, CLEAR-IT-2, assessing PRN dosing after 4 monthly loading doses, followed by Phase 3 testing that included a treatment arm of 3 monthly injections followed by

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dosing every 8 weeks (Ex.1002, ¶58; Ex.1006, 1576)—the precise dosing regimen Regeneron claimed in the '572 patent application filed almost three years later.

B. PETITIONER'S PRIOR ART REFERENCES[4]

Petitioner's prior art relates to the following clinical trials:

Trial	Name	Prior Art	Dosage Regimen
Phase 1 (AMD)	CLEAR-IT-1	Dixon, Nguyen-2006, Nguyen-2009	Single dose
Phase 2 (AMD)	CLEAR-IT-2	Dixon, Heier-2009	Monthly or quarterly doses through wk-12, followed by PRN
Phase 3 (AMD)	VIEW 1; VIEW 2	Dixon; NCT-795 NCT-377; Regeneron (8-May-2008)	Three monthly doses, followed by bi-monthly doses (2 mg)

[4] The asserted prior art references all qualify as publications that were available to—and indeed cited by—interested, skilled artisans before the '572 patent's earliest, purported priority date (i.e., January 13, 2011). (Ex.1002, ¶¶72-124; Ex.1006, 1579 (citing NCT Studies); Ex.1007, 268 (citing Regeneron Press Releases)).

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The dosing regimen disclosed in the aforementioned Phase 3 trials involved an "initial dose" at day 0; two "secondary doses" administered at weeks 4 and 8; followed by "tertiary doses" administered every eight weeks after the preceding dose (i.e., weeks 16, 24, 32, 40, etc.).

1. Dixon (Ex.1006)

Dixon published in 2009 and thus constitutes prior art under 35 U.S.C. § 102(b). Regeneron has confirmed that "Dixon was publicly accessible in print by October 2009, and online by August 20, 2009." *Regeneron Pharms., Inc. v. Novartis Pharma AG*, IPR2021-00816, Paper No. 1, 23 (Apr. 16, 2021).

Dixon teaches that VEGF Trap-Eye is an "anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." Ex.1006, 1573; Ex.1002, ¶144. Dixon also discloses pertinent details regarding Phase 3 trials (VIEW1/VIEW2) and the dosing regimens used therein. *Id.*, 1573, 1575-76, 1579 (Bibliography Nos. 46-47); Ex.1002, ¶¶136-138. Dixon states the "time and financial burden of monthly injections" led researchers "to examine the efficacy of alternative dosing schedules." Ex.1006, 1574. Identifying the problem of the "significant time and financial burden [that] falls on patients during their treatment course" of monthly injections of drugs such as ranibizumab, and the desirability of "decreased dosing intervals," Dixon reports that

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"[t]he development of new drugs for neovascular AMD has thus focused on both improving efficacy and extending duration of action." Ex.1006, 1574, 1577.

Dixon discloses the Phase 3 VIEW1/VIEW2 dosing regimens, which, as illustrated below, fall squarely within the scope of the Challenged Claims:

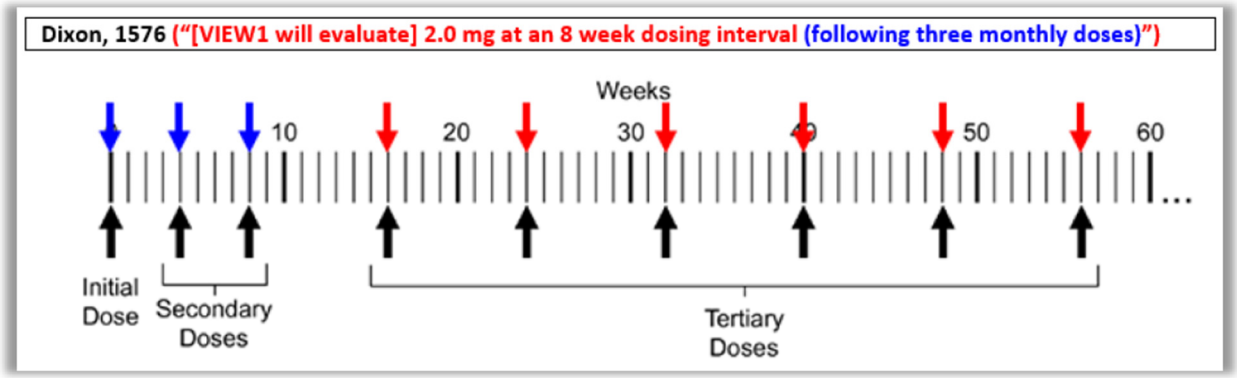

Figure 1. (Modified from Fig.1 of the '572 patent).

Dixon's disclosure of an "8 week dosing interval (following three monthly doses)," means that three monthly doses (**blue arrows**) were to be administered, followed by injections at eight week intervals thereafter (**red arrows**). *See* Ex.1006, 1576; Ex.1002, ¶¶136-137. Dixon also discloses the promising results of the Phase 2 CLEAR-IT-2 study of VEGF Trap-Eye in AMD. Ex.1006, 1576.

2. Regeneron (8-May-2008) (Ex.1009)

Regeneron (8-May-2008) published on May 8, 2008, and thus constitutes prior art under 35 U.S.C. § 102(b).

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Regeneron (8-May-2008) reports VIEW1/VIEW2 Phase 3 AMD trials and sets out the dosing regimen encompassed by the Challenged Claims: "In the first year, the VIEW2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at 2.0 mg at an 8-week dosing interval, ***including one additional 2.0 mg dose at week four*** [i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**]." Ex.1009, 1 (emphasis added); Ex.1002, ¶160.

Regeneron (8-May-2008) also reports that "[r]esults from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision." Ex.1009, 1; Ex.1002, ¶158.

3. NCT-795 (Ex.1010)

NCT-795 is an on-line electronic publication disclosing the VIEW1 regimen Regeneron submitted to the ClinicalTrials.gov database maintained by the National Library of Medicine at the National Institutes of Health ("NIH"). ClinicalTrials.gov is a website "***intended for a wide audience***, including individuals with serious or life-threatening diseases or conditions, members of the public, ***health care providers, and researchers***." Ex.1021, 2 (emphasis added). After Congress passed the Food and Drug Modernization Act of 1997, which required "a public information resource on certain clinical trials," NIH created ClinicalTrials.gov in 2000. *Id.*

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As shown in the following, NCT-795 is a § 102 printed publication. *See Hulu, LLC v. Sound View Innovations*, No. IPR2018-01039, 2019 WL 7000067, *5 (P.T.A.B. Dec. 20, 2019).

NCT-795 (an electronic publication) "was accessible to persons concerned with the art to which the document relates." MPEP § 2128. In fact, the Board has found a ClinicalTrials.gov printout analogous to NCT-795 qualifies as a prior art printed publication. *Grünenthal GMBH v. Antecip Bioventures II LLC*, No. PGR2019-00026, 2020 WL 4341822, *8 (P.T.A.B. May 5, 2020).

Here, the evidence confirms that NCT-795—including the VIEW1 dosing regimen and other clinical study details provided therein—was publicly available on the ClinicalTrials.gov website prior to January 13, 2011. First, the History of Changes archive that ClinicalTrials.gov maintains for each study demonstrates the VIEW1 regimen was disclosed to the public before 2011. Ex.1010, 8. Second, Wayback Machine records and the corresponding affidavit provided in related proceedings, a copy of which is provided herein (Ex.1022, 1-2, 8-11) show NCT-795's public availability prior to 2011.[5] *Sandoz Inc. v. Abbvie Biotechnology Ltd.*, No. IPR2018-00156, 2018 WL 2735468, *4-5 (P.T.A.B. June 5, 2018) (finding Wayback Machine screenshot and expert testimony adequate evidence to establish

[5] Patent Owner did not challenge the public availability of NCT-795 in the related proceedings, IPR2021-00880 or IPR2021-00881.

FDA website as a prior art printed publication). Third, NCT-795 was expressly cited in the prior art itself (*e.g.*, Ex.1006, 1579 (Bibliography No. 46) ("Accessed 28 Sep 2008"); Ex.1020, 94-95), demonstrating its actual publication and availability to interested, skilled artisans in at least September 2008. Ex.1002, ¶¶117-122.

Finally, in support of this Petition, Dr. Tanna declares that in his experience and expert opinion that clinical study details were publicly accessible from ClinicalTrials.gov to skilled artisans—who were both interested in and familiar with such reports—as of their posted dates. Ex.1002, ¶¶108-116,123. As such, NCT-795 is a printed publication that was accessible to the relevant public more than one year before January 13, 2011 and constitutes prior art under 35 U.S.C. § 102(b).

NCT-795 discloses Regeneron's Phase 3 VIEW1 trial. Ex.1010, 3-5. Specifically, NCT-795 discloses the treatment arms of the VIEW1 study, including the every-8-week treatment regimen: "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." Ex.1010, 4-5, 8; Ex.1002, ¶¶184-185 (i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, 48**, etc.).

4. NCT-377 (Ex.1011)

NCT-377, like NCT-795 (above), is an on-line electronic publication from NIH's ClinicalTrials.gov website describing the VIEW2 Study. As shown, NCT-

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377 is also a § 102 printed publication. *Hulu*, 2019 WL 7000067, *5; *see also Grünenthal*, 2020 WL 4341822, at *8.

Each of the following independently confirm that NCT-377 (including the study details and dosing regimen provided therein) was publicly available and accessible to interested, skilled artisans prior to January 13, 2011 (MPEP § 2128): (i) the History of Changes archive for NCT-377 (Ex.1011, 1-3); (ii) the Wayback Machine records and the corresponding affidavit provided in related proceedings, a copy of which is provided herein (Ex.1022, 1-2, 4-7, 11; *see Sandoz*, 2018 WL 2735468, at *4-5)[6]; (iii) prior art references expressly citing NCT-377 (Ex.1006, 1579 (Bibliography No. 47) ("Accessed 28 Sep 2008"); Ex.1020, 95-96); and (iv) Dr. Tanna's declaration, providing his experience and expert opinion. Ex.1002, ¶¶108-123. As such, NCT-377 constitutes prior art under 35 U.S.C. § 102(b).

NCT-377 describes Regeneron's VIEW2 trial: "a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration." Ex.1011, 5. NCT-377 discloses the treatment arms for the VIEW2 trial, including the every-8-week dosing regimen: "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0

[6] Patent Owner did not challenge the public availability of NCT-377 in the related proceedings, IPR2021-00880 or IPR2021-00881.

mg dose at Week 4) during the first year [i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**]." Ex.1011, 5-6 (emphasis added); Ex.1002, ¶¶184-185.

5. Hecht (Ex.1025)

Hecht published in 1995, and thus constitutes prior art under 35 U.S.C. § 102(b). To Petitioner's knowledge, Hecht was neither submitted nor cited during prosecution, and thus never considered by the Examiner. Ex.1001, References Cited.

Hecht is a chapter in *Remington: The Science and Practice of Pharmacy*, Volume II, published in 1995. Hecht is focused on ophthalmic preparations and considerations a POSA should be aware of when formulating a preparation to be administered to the eye. Among other things, Hecht teaches that ophthalmic solutions "are formulated to be sterile, isotonic and buffered for stability and comfort." Ex.1025, 1569. Additionally, Hecht teaches that "[t]he use of various additives in ophthalmic solutions," while limited, can include "nonionic surfactants" because they are "least toxic to the ophthalmic tissues." *Id.* at 1571.

XII. GROUNDS FOR UNPATENTABILITY

A. ANTICIPATION

The Challenged Claims are anticipated by each of Dixon, Regeneron (8- May-2008), NCT-795, and NCT-377. Each reference discloses all limitations of the Challenged Claims, expressly and/or inherently.

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1. Legal standards

Anticipation requires that a "single prior art reference disclose[], either expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002).

An inherent disclosure requires that "the natural result flowing from the operation as taught would result in the performance of the questioned function." *King Pharms*, 616 F.3d at 1275. Newly discovered results or new benefits of a known process directed to the same purpose are not patentable. *Id.*; *In re Omeprazole*, 483 F.3d at 1373; *Perricone*, 432 F.3d at 1378. Said another way, where a method has already been "disclosed to the public," meaning when the "prior art discloses the steps of a process, and…[the patentee] did not 'manipulate or otherwise alter the basic application'… disclosed in the prior art[,]" then the patentee cannot claim as a new invention the 'unexpected or unappreciated results from' that method. *Bristol*, 86 F. Supp. 2d at 443, *aff'd in relevant part*, 246 F.3d 1368. This is true, even when a prior art reference does not establish the effectiveness of a disclosed method. *Bristol*, 246 F.3d at 1376.

In addition, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol*, 246 F.3d at 1379. To be enabling for purposes of

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anticipation, however, a reference need not prove efficacy of a disclosed method. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

2. Ground 1: Dixon anticipates Claims 1-5, 8-11, 14, and 26-30

a. Independent Claims 1, 26, and 29

Claim 1 is directed to a method of treating an angiogenic eye disorder in a patient in need thereof. The clinical trials described by Dixon provide a method of treating AMD[7]:

- "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, 1573
- "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." *Id.*, 1577
- "[P]atients...demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." *Id.*
- Phase 2 patients "treated with 2.0 mg or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p<0.0001$) and 5.4

[7] AMD is an angiogenic eye disorder. Ex.1001, 5:30-48.

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($p<0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks." *Id.*, 1576.

- "Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye." *Id.*, 1577-78 (describing DME and RVO studies)).

The claims recite the following active method steps:

- sequentially administering to the patient by intravitreal injection a single **initial dose** of 2 mg of aflibercept, followed by one or more **secondary doses** of 2 mg of aflibercept, followed by one or more **tertiary doses** of 2 mg of aflibercept;
- wherein each secondary dose is administered approximately **4 weeks** following the immediately preceding dose; and
- wherein each tertiary dose is administered approximately **8 weeks** following the immediately preceding dose"

Ex.1001, Claim 1 (emphasis added).

Dixon discloses the Phase 3 VIEW1/VIEW2 dosing regimens, which, as illustrated below, fall squarely within the scope of the Challenged Claims:

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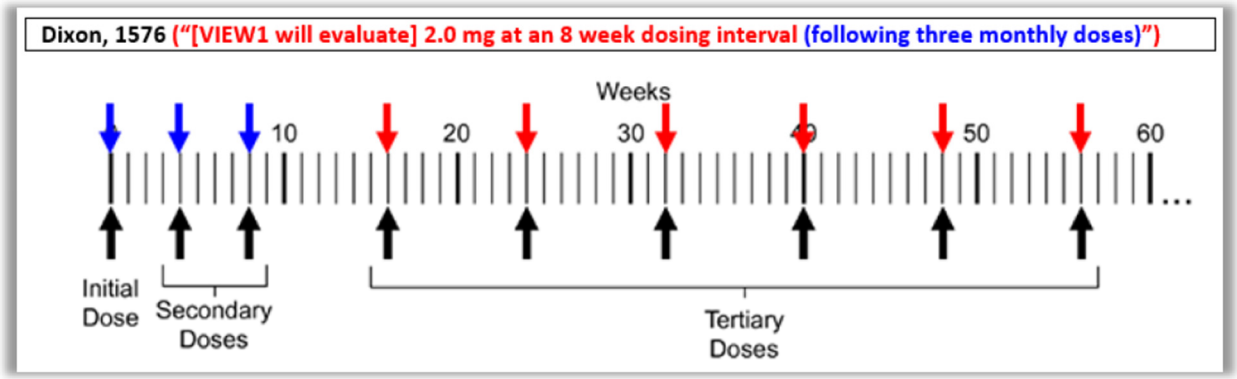

Figure 1. (Modified from Fig.1 of the '338 patent).

Dixon's disclosure of an "8 week dosing interval (following three monthly doses)," means that three monthly doses (**blue arrows**) were to be administered, followed by injections at eight week intervals thereafter (**red arrows**). Ex.1006, 1576; Ex.1002, ¶137. Dixon further teaches that aflibercept is administered intravitreally. Ex.1006, 1575, 1576; Ex.1002, ¶137.

The active ingredient tested in Dixon is the same active ingredient recited in the claims of the '572 patent. Ex.1002, ¶138. The active ingredient recited in the claimed dosage regimen is "aflibercept." According to the specification, "aflibercept" means a "VEGF antagonist… [that] is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules." Ex.1001, 2:51-56. The specification of the '572 patent states that the term "aflibercept" and "VEGFR1R2-FcΔC1(a)" are two terms that refer to the same "exemplary VEGF antagonist." *Id.* The Examples in the '572 patent describe the

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same Phase 3 clinical trial described in Dixon, using aflibercept (referred to in the examples as VEGFT). Ex.1001, Example 4, and 5:23-26. These are the same clinical trials that supported the FDA approval of aflibercept.

The last clause of claim 1 relates to the efficacy achieved through the claimed dosage regimen. As discussed above in Section IX.C, this statement of intended result is not given patentable weight because it does not alter the claimed method. However, even if the Board finds that this last element should be given patentable weight, Dixon still anticipates. The claim states that the "patient achieves a gain in visual acuity within 52 weeks following the initial dose." For the reasons discussed below, Dixon inherently anticipates this element.

Dixon teaches that the clinical trials sought to assess the improvements in visual acuity throughout the study period. Ex.1006, 1576; Ex.1002, ¶140. Dixon reports the favorable results of the phase 2 clinical trial, where the patients achieved a gain in visual acuity within 52 weeks following the initial dose. *Id.*

Subsequent to the favorable phase 2 results, Regeneron continued onto phase 3. Dixon disclosed the details of that phase 3 trial and noted that the primary outcome will be the proportion of patients who maintain vision at week 52. Ex.1006, 1576, Ex.1002, ¶141. Although final results of the phase 3 clinical trial were not reported in the literature until after the priority date of the '572 patent, Dixon's description of the trial protocol nevertheless anticipates the present claims. The

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Federal Circuit has "repeatedly held that 'newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent.'" *In re Montgomery*, 677 F.3d at 1381 (holding that clinical data obtained from a known method of administering a known compound to treat a known indication is not patentable because "efficacy is inherent in carrying out the claim steps."). "[O]ne cannot obtain a valid patent on a known use of a known process that has been described in the literature more than one year prior to the date of one's invention. Such processes are old, regardless of the relative success of the prior and later participants." *Bristol*, 246 F.3d at 1380; *see also Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F. 2d 628, 633 (Fed. Cir. 1987) (explaining that the burden to proving anticipation of a method is "limited to establishing that [the prior art] disclosed the same process," and the burden does not include establishing that the prior art "recognized the…capabilities" of the process).

Dixon is enabling for purposes of anticipation because it describes the claimed methods of treatment with sufficient detail such that a POSA would be able to carry out the claimed methods. Ex.1002, ¶143; *Impax Labs. Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006). Based on Dixon's description of the aflibercept Phase 3 clinical trials (VIEW 1/VIEW 2), and the results of the Phase 2 trials (CLEAR-IT-2), a POSA would have known how to administer, what dosing

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schedule to follow, and how much aflibercept to administer to a patient to treat angiogenic eye disorders. Ex.1002, ¶143. Accordingly, Dixon anticipates claim 1.

The following table (confirmed by Dr. Tanna), show how Dixon discloses each and every element of claim 1:

Claim 1:	**Dixon:**
A method of treating an angiogenic eye disorder in a patient in need thereof,	"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, 1573. "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." *Id.*, 1573, 1577. Phase 2 patients "treated with 2.0 mg or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p<0.0001$) and 5.4 ($p<0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks." *Id.*, 1576. "[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." *Id.*, 1577. "Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly

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	VEGF Trap-Eye." *Id.*, 1577-78 (describing DME and RVO studies). Ex.1002, ¶144.
comprising sequentially administering to the patient by intravitreal injection a **single initial dose** of 2 mg of aflibercept, followed by one or more **secondary doses** of 2 mg of aflibercept, followed by one or more **tertiary doses** of 2 mg of aflibercept;	"[Phase 3] will evaluate the safety and efficacy of . . . 2.0 mg at an 8 week dosing interval (***following three monthly doses***)." Ex.1006, 1576 (emphasis added). In other words, an "initial dose" at day 0, "secondary doses" at weeks 4 and 8; and "tertiary doses" of every 8 weeks beginning at week 16 (i.e., doses at week **0, 4, 8**, **16, 24, 32, 40, and 48**). Ex.1002, ¶144.
wherein each secondary dose is administered approximately **4 weeks** following the immediately preceding dose; and	*Id.*
wherein each tertiary dose is administered approximately **8 weeks** following the immediately preceding dose;	*Id.*
wherein the patient achieves a gain in **visual acuity within 52 weeks** following the initial dose.	Not given patentable weight. See Section IX.C.

The analysis for independent **Claims 26 and 29** is nearly identical. First, the dosing regimen elements are the same, which Dixon anticipates for the reasons stated above. The only differences between claims 26 and 29 and claim 1 is the identification of the disease to be treated (broader angiogenic eye disorder in claim

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1 vs. AMD in claims 26 and 29) and the particular non-limiting endpoint of the treatment. As shown below, Dixon similarly anticipates claims 26 and 29:

Claim 26:	**Dixon:**
26. A method of treating **age related macular degeneration** in a patient in need thereof…	"Age-related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 90% of patients with AMD have the dry form, neovascular AMD accounts for the vast majority of patients who develop legal blindness. Until recently, few treatment options existed for treatment of neovascular AMD. The advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD." Ex.1006, 1573. "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." *Id.*, 1573, 1577. "Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye." *Id.*, 1577-78 (describing DME and RVO studies). Ex.1002, ¶145.
wherein the method is **as effective** in **achieving a gain** in **visual acuity** as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related	Not given patentable weight. See Section IX.C. Alternatively, this element is inherently anticipated for the

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macular degeneration at 52 weeks following the initial dose.	same reasons as in claim 1 above. *Bristol*, 246 F.3d at 1380. [8]
Claim 29:	**Dixon:**
29. A method of treating **age-related macular degeneration** in a patient in need thereof…	"Age-related macular degeneration (AMD) affects > 14 million individuals worldwide. Although 90% of patients with AMD have the dry form, neovascular AMD accounts for the vast majority of patients who develop legal blindness. Until recently, few treatment options existed for treatment of neovascular AMD. The advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD." Ex.1006, 1573. "VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." *Id.*, 1573, 1577. "Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye." *Id.*, 1577-78 (describing DME and RVO studies). Ex.1002, ¶145.
wherein the method is **as effective** in **maintaining visual acuity** as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human	Not given patentable weight. See Section IX.C. Alternatively, this element is inherently anticipated for the

[8] Dixon teaches that the Phase 3 trial is a non-inferiority study comparing the efficacy of aflibercept to 0.5 mg ranibizumab. Ex.1006, 1576.

subjects with age-related macular degeneration at 52 weeks following the initial dose.	same reasons as in claim 1 above. *Bristol*, 246 F.3d at 1380.[9]

b. Dependent claims 2-5, 8-11, 14, 27, 28, and 30

Claims 5, 11, and 27 further limit the claimed dosing regimen as follows: "wherein only two secondary doses are administered to the patient"— i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. Dixon expressly discloses this exact regimen, i.e., an initial dose at day 0 and two secondary doses at weeks 4 and 8. Ex.1006, 1576 ("three monthly doses"), Ex.1002, ¶146; *also* Fig.1 (*supra* § X(B)(1) (**blue arrows**)). Accordingly, Dixon anticipates.

Claims 2-4, 8-10, 28, and 30 are all directed to specific effects achieved by following the dosing method disclosed in the prior art. As described above in Section IX.C, none of these specific effects should be given patentable weight. Accordingly, Dixon anticipates these claims.

However, even if the Board disagrees and gives the specific effects recited in these dependent claims patentable weight, Dixon still inherently anticipates. As noted above, Dixon reported the positive results of the Phase 2 trial, showing that repeated intravitreal injections of aflibercept resulted in gains in visual acuity

[9] Dixon teaches that the Phase 3 trial is a non-inferiority study comparing the efficacy of aflibercept to 0.5 mg ranibizumab. Ex.1006, 1576.

Ex.1006, 1576; Ex.1002, ¶148. While Dixon did not disclose the final results of the phase III trial showing the various efficacy claimed in claims 2, 3, 8, 10, 28, and 30 (e.g., "gains at least 7 letters" (or 8 or 9 letters) or "maintaining visual acuity [as compared to monthly administration of ranibizumab]"), or the speed at which patients achieved this efficacy as claimed in claims 4 and 9 (e.g., "gain in visual acuity within 24 weeks following the initial dose"), the "mere[] propos[al]" of a method at an advanced state of testing designed to secure regulatory approval (without yet having results) is sufficient to anticipate. *In re Montgomery*, 677 F.3d at 1382 (rejecting argument that none of the references demonstrated that the active *actually* achieved the claimed efficacy because an anticipating reference need not have "actual creation or reduction to practice" but instead only needs "an enabling disclosure" (internal citations omitted)). This is why "[i]t is well established that a patent may be secured, and typically is secured, before the conclusion of clinical trials." *Id.*

Here, Dixon teaches the exact method of the claims, and teaches the use of the method for the identical purpose (i.e., the use of aflibercept to treat angiogenic eye disorder).

Claim 14 specifies that the patients to be treated will exclude patients that have active ocular inflammation and active ocular or periocular infection. As noted above, the exclusion criteria are not entitled to patentable weight, and thus are unable

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to distinguish the claims from the prior art. Therefore, for the same reasons that claim 1 is anticipated, claim 14 is likewise anticipated.

Moreover, Dixon's disclosure of the details surrounding the Phase 3 aflibercept trial inherently discloses these claim elements.

A POSA would know that the Phase 3 trial disclosed by Dixon would necessarily exclude patients having active ocular inflammation or active ocular or periocular infection. Ex.1002, ¶151.

The LUCENTIS (ranibizumab) trials excluded people with "[a]ctive intraocular inflammation (grade trace or above) in the study eye" and "[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye." Ex.1026, Supplemental Appendix; *also*, Ex.1019, 2; Ex.1002, ¶152.

Additionally, a POSA would understand that patients having active ocular inflammation or active ocular or periocular infection should be excluded from intravitreal injection treatment. Ex.1032, 76, 81, 85; Ex. 1002, ¶153. Moreover, it was known that intravitreal injections presented further complications for such patients. Ex.1006, 1577; Ex.1033, 677; Ex.1032, 67, 69, 74-75; Ex.1014, 2537; *see* Ex.1002, ¶153.

As the aflibercept trial was set up as a non-inferiority study comparing the effectiveness of aflibercept to the effectiveness of ranibizumab, a POSA would know

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that in order to have a meaningful head-to-head statistical comparison of the VIEW aflibercept arms with monthly ranibizumab, the outcomes of the MARINA and ANCHOR trials would have a very similar patient population in the VIEW trials. A clinical study designer/investigator would understand that the way to do this is to adopt the same, or very similar, inclusion/exclusion criteria as those used in the comparator study, in this case MARINA and ANCHOR. Ex.1002, ¶154; *also* Ex.1014.[10] The FDA guidance on non-inferiority studies explains that it is important to have a sufficiently similar study design, including characteristics of the patient population, so that the current study can be sufficiently compared to the historical studies on the active control. Ex.1031 at 15-16. Thus, a POSA would understand that the clinical trial disclosed in Dixon necessarily excluded people with active intraocular inflammation or active eye infections.

Further, Dixon cites to a number of articles which provide additional details regarding the aflibercept trials. In one of the cited references, Nguyen 2006, exclusion criteria for the Phase 3 trial are listed. One of the exclusion criteria is identified as "[p]resence of a disease other than NVAMD in the study eye that could affect vision or safety assessments." Ex.1023, 3; *also* Ex.1005, Table 1. A POSA would understand that the presence of active ocular inflammation and active ocular

[10] Heier 2012 also confirms that the Phase 3 trial did, in fact, exclude patients with "Active intraocular inflammation in either eye" or "Active ocular or periocular infection in either eye." Ex.1030 (Appendix 2).

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or periocular infection would be such a condition that "could affect vision or safety assessments." Ex.1002, ¶155. As discussed above, the presence of active inflammation or infection is contraindicated with treatment administered through intravitreal injection.

Thus, a POSA would understand that the clinical trial disclosed in Dixon excluded the patients described in claim 14. Accordingly, Dixon anticipates claim 14.

3. Ground 2: Regeneron (8-May-2008) anticipates Claims 1-5, 8-11, 14, and 26-30

a. Independent Claims 1, 26, and 29

Regeneron (8-May-2008) describes Phase 2 and 3 trials of aflibercept (referred to as VEGF Trap-Eye) in AMD using the claimed dosing regimens—disclosing all limitations and thus anticipating the Challenged Claims. Ex.1002, ¶¶157-159.

The clinical trials described by Regeneron (8-May-2008) provide a method of treating AMD:

- "Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision." Ex.1009, 1.

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- "VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart)." *Id.*, 1-2.
- "Dosing of the first patient in this confirmatory Phase 3 trial is an important milestone for this compound intended to treat a devastating ocular disease that impacts millions of people worldwide." *Id.*, 1.

Regeneron (8-May-2008) teaches the claimed dosage regimen. Regeneron (8-May-2008) teaches that the Phase 3 trial will use intravitreal injection. Ex.1009, 1. Also, Regeneron (8-May-2008) teaches that the Phase 3 VIEW2 "study will evaluate the safety and efficacy of VEGF Trap-Eye at . . . *2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four*," (Ex.1009, 1 (emphasis added)); in other words, doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. Ex.1002, ¶160.

The active ingredient recited in the claimed dosage regimen is "aflibercept." The specification teaches that "aflibercept" means a "VEGF antagonist… [that] is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules." Ex.1001, 2:51-56. The specification of the '572 patent states that the term "aflibercept" and "VEGFR1R2-FcΔC1(a)" are two terms that refer to the same "exemplary VEGF antagonist." *Id.* The Examples in the '572 patent

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describe the same clinical trials described in Regeneron (8-May-2008), using aflibercept (referred to in the examples as VEGFT). Ex.1001, Example 4, and 5:23-26. These are the same clinical trials that supported the FDA approval of aflibercept. Ex.1002, ¶161.

The last clause of claim 1 relates to the efficacy achieved through the claimed dosage regimen. As discussed above in Section IX.C, this statement of intended result is not given patentable weight because it does not alter the active steps of the claimed method.

Even if the Board disagrees that this last element should not be given patentable weight, Regeneron (8-May-2008) still anticipates. Ex.1002, ¶163-165. The claim states that the "patient achieves a gain in visual acuity within 52 weeks following the initial dose." Regeneron (8-May-2008) inherently anticipates this element.

Regeneron (8-May-2008) reports the favorable results of the phase 2 clinical trial. Ex.1002, ¶164; Ex.1009, 1 ("Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision.'); *also id.*, 1-2 ("VEGF Trap-Eye met both primary and secondary key endpoints"). Subsequent to the favorable phase 2 results, Regeneron continued onto phase 3. Regeneron (8-May-2008) disclosed the details of that Phase 3 trial

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and noted that the primary outcome will be the proportion of patients who maintain vision at the end of one year. *Id.*

Although final results of the Phase 3 clinical trial were not reported in the literature until after the priority date of the '572 patent, Regeneron (8-May-2008)'s disclosure of the trial protocol nevertheless anticipates the present claims. Ex.1002, ¶165. The caselaw is clear that "newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *In re Montgomery*, 677 F.3d at 1381; *also Bristol*, 246 F.3d at 1380; *also Verdegaal*, 814 F. 2d at 633.

Regeneron (8-May-2008) is enabling because it describes the claimed methods of treatment with sufficient detail such that a POSA would be able to carry out the claimed methods. Ex.1002, ¶165; *Impax Labs*, 468 F.3d at 1383. Based on Regeneron (8-May-2008)'s description of the aflibercept Phase 3 clinical trials (VIEW 1 and VIEW 2), and the results of the Phase II trials (CLEAR-IT-2), a POSA would have known how to administer, what dosing schedule to follow, and how much aflibercept to administer to a patient to treat angiogenic eye disorders. Ex.1002, ¶165. Accordingly, Regeneron (8-May-2008) anticipates claim 1.

The following table (confirmed by Dr. Tanna, shows how Regeneron (8-May-2008) discloses each element of claim 1:

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Claim 1:	Regeneron (8-May-2008):
A method of treating an angiogenic eye disorder in a patient in need thereof,	"Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision." Ex.1009, 1. "VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart)." *Id.*, 1-2. "Dosing of the first patient in this confirmatory Phase 3 trial is an important milestone for this compound intended to treat a devastating ocular disease that impacts millions of people worldwide." *Id.*, 1. Ex.1002, ¶166.
comprising sequentially administering to the patient by intravitreal injection a **single initial dose** of 2 mg of aflibercept, followed by one or more **secondary doses** of 2 mg of aflibercept, followed by one or more **tertiary doses** of 2 mg of aflibercept;	The Phase 3 VIEW2 "study will evaluate the safety and efficacy of VEGF Trap-Eye at . . . *2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four*." Ex.1009, 1 (emphasis added). In other words, doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. Ex.1002, ¶166.

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wherein each secondary dose is administered approximately **4 weeks** following the immediately preceding dose; and	*Id.*
wherein each tertiary dose is administered approximately **8 weeks** following the immediately preceding dose;	*Id.*
wherein the patient achieves a gain in **visual acuity within 52 weeks** following the initial dose.	Not given patentable weight. See Section IX.C.

The analysis for independent **Claims 26 and 29** is nearly identical. First, the dosing regimen elements are the same, which Regeneron (8-May-2008) anticipates for the reasons stated above. The only differences between claims 26 and 29 and claim 1 is the identification of the disease to be treated (broader disorder in claim 1 vs. AMD in claims 26 and 29) and the particular non-limiting endpoint of the treatment. As shown below, Regeneron (8-May-2008) anticipates claims 26 and 29:

Claim 26:	Regeneron (8-May-2008)
26. A method of treating **age related macular degeneration** in a patient in need thereof…	Regeneron (8-May-2008) discloses, Phase 3 trials directed to AMD patients. Ex.1009.
wherein the method is **as effective** in **achieving a gain** in **visual acuity** as monthly administration of 0.5 mg of ranibizumab… at 52 weeks following the initial dose.	Not given patentable weight. See Section IX.C. Alternatively, this element is inherently anticipated for the

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	same reasons as in claim 1 above. *Bristol*, 246 F.3d at 1380. [11] Ex.1002, ¶167.
Claim 29:	**Regeneron (8-May-2008)**
29. A method of treating **age-related macular degeneration** in a patient in need thereof…	Regeneron (8-May-2008) discloses, Phase 3 trials directed to AMD patients. Ex.1009.
wherein the method is **as effective** in **maintaining visual acuity** as monthly administration of 0.5 mg of ranibizumab …at 52 weeks following the initial dose.	Not given patentable weight. See Section IX.C. Alternatively, this element is inherently anticipated for the same reasons as in claim 1 above. [12] Ex.1002, ¶167.

b. Dependent claims 2-5, 8-11, 14, 27, 28, and 30

Claims 5, 11, and 27 further limit the claimed dosing regimen as follows: "wherein only two secondary doses are administered to the patient"— i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. Regeneron (8-May-2008) expressly discloses "8-week dosing interval, including one additional 2.0 mg dose at week four"—i.e., a single initial dose (week 0) plus two secondary doses administered four weeks apart (weeks 4 and 8). Ex.1009, 1; Ex.1002, ¶168. Accordingly, Regeneron (8-May-2008) discloses the added limitations, and anticipates.

[11] Regeneron (8-May-2008) teaches that the Phase 3 trial is a non-inferiority study comparing the efficacy of aflibercept to 0.5 mg ranibizumab. Ex.1009, Regeneron (8-May-2008).

[12] Regeneron (8-May-2008) teaches that the Phase 3 trial is a non-inferiority study comparing the efficacy of aflibercept to 0.5 mg ranibizumab. Ex.1009, Regeneron (8-May-2008).

Claims 2-4, 8-10, 28, and 30 are directed to specific effects achieved by following the dosing method disclosed in the prior art. As described in Section IX.C, none of these specific effects should be given patentable weight. Accordingly, Regeneron (8-May-2008) anticipates these claims.

However, even if the Board gives the specific effects recited in these dependent claims patentable weight, Regeneron (8-May-2008) still inherently anticipates. Ex.1002, ¶170-171. Regeneron (8-May-2008) reported the positive results of the phase 2 trial, showing that repeated intravitreal injections of aflibercept resulted in gains in visual acuity. Ex. 1009; Ex.1002, ¶170. While Regeneron (8-May-2008) did not disclose the final results of the phase III trial showing the various efficacy claimed in claims 2, 3, 8, 10, 28, and 30, or the speed at which patients achieved this efficacy as claimed in claims 4 and 9, the disclosure still anticipates. *In re Montgomery*, 677 F.3d at 1382.

Here, Regeneron (8-May-2008) teaches the exact method of the claims, and use of the method for the identical purpose (i.e. the use of aflibercept to treat angiogenic eye disorder). Ex.1002, ¶171.

Claim 14 specifies that the patients to be treated will exclude patients that have active ocular inflammation and active ocular or periocular infection. As noted above, the exclusion criteria are not entitled to patentable weight, and thus are unable

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to distinguish the claims from the prior art. Therefore, for the same reasons that claim 1 is anticipated, claim 14 is likewise anticipated.

Notwithstanding, Regeneron (8-May-2008)'s disclosure of the details surrounding the Phase 3 aflibercept trial inherently discloses these claim elements.

A POSA would know that the Phase 3 trial disclosed by Regeneron (8-May-2008) would necessarily exclude patients having active ocular inflammation or active ocular or periocular infection. Ex.1002, ¶174.

First, the ranibizumab trials excluded people with "[a]ctive intraocular inflammation (grade trace or above) in the study eye" and "[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye." Ex.1002, ¶175; Ex.1026, at Supplemental Appendix; *also*, Ex.1019, 2.

Additionally, a POSA would understand that patients having active ocular inflammation or active ocular or periocular infection should be excluded from intravitreal injection treatment. Ex.1032, 76, 81, 85; Ex. 1002, ¶176. Moreover, it was known that intravitreal injections presented further complications for such patients. Ex.1006, 1577; Ex.1033, 677; Ex.1032, 67, 69, 74-75; Ex.1014, 2537; Ex.1002, ¶176.

As the aflibercept trial was set up as a non-inferiority study comparing the effectiveness of aflibercept to the effectiveness of ranibizumab, a POSA would know

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that in order to have a meaningful head-to-head statistical comparison of the VIEW aflibercept arms with monthly ranibizumab, and the outcomes of the MARINA and ANCHOR trials would necessitate having a very similar patient population in the VIEW trials. Ex.1002, ¶177. A clinical study designer/investigator would understand that the way to do this is to adopt the same, or very similar, inclusion/exclusion criteria as those used in the comparator study, in this case MARINA and ANCHOR. *Id.*; *also* Ex.1014.[13] The FDA guidance on non-inferiority studies explains that its important to have a sufficiently similar study design, including characteristics of the patient population, so that the current study can be sufficiently compared to the historical studies on the active control. Ex.1031, 15-16. Thus, a POSA would understand that the clinical trial disclosed in Regeneron (8-May-2008) necessarily excluded people with active intraocular inflammation or active eye infections. Ex.1002, ¶177

Additionally, by the earliest filing date of the '572 patent, additional details regarding the Phase 3 trials were made public—informing a POSA of these additional details. Ex.1002, ¶178. For example, in Nguyen-2006, exclusion criteria for the Phase 3 trial are listed. One of the exclusion criteria is identified as "[p]resence of a disease other than NVAMD in the study eye that could affect vision

[13] Heier 2012 also confirms that the Phase 3 trial did, in fact, exclude such patients. Ex.1030 (Appendix 2).

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or safety assessments." Ex.1023, 3; *also* Ex.1005, Table 1. A POSA would understand that the presence of active ocular inflammation and active ocular or periocular infection would be such a condition that "could affect vision or safety assessments." Ex.1002, ¶178. And as discussed above, the presence of active inflammation or infection is contraindicated with treatment administered through intravitreal injection.

Thus, a POSA would understand that the clinical trial disclosed in Regeneron (8-May-2008) excluded the patients described in claim 14. Ex.1002, ¶179. Accordingly, Regeneron (8-May-2008) anticipates claim 14.

4. Grounds 3 and 4: NCT-795 and NCT-377 each anticipate Claims 1-5, 8-11, 14, and 26-30

a. Independent Claims 1, 26, and 29

NCT-795 and NCT-377 describe the Phase 3 VIEW1/VIEW2 trials studying aflibercept for treating the angiogenic eye disorder AMD—thereby disclosing all limitations and thus anticipating the Challenged Claims.

The clinical trials described by both NCT-795 and NCT-377 provide a method of treating AMD:

Claim 1:	**NCT-795:**	**NCT-377:**
A method of treating an angiogenic eye disorder in a patient in need thereof,	"A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy,	"A Randomized, Double Masked, Active Controlled Phase 3 Study of the Efficacy, Safety,

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	Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With [AMD]." Ex.1010, 3, 4.	and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With [AMD]." Ex.1011, 3.
	Ex.1002, ¶181.	

NCT-795 and NCT-377 each disclose the claimed dosage regimen to be administered through intravitreal injections.

NCT-795:	**NCT-377:**
"Official Title: A Randomized, Double Masked, Active Controlled, Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD)." Ex.1010, 3. "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." Ex.1010, 8.	"Official Title: A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." Ex.1011, 3-4. "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year." Ex.1011, 6.
In other words, an "initial dose" at day 0, "secondary doses" at weeks 4 and 8; and "tertiary doses" every 8 weeks beginning at week 16 (i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**). Ex.1002, ¶183-184.	

The active ingredient recited in the claimed dosage regimen is "aflibercept." The specification teaches that "aflibercept" means a "VEGF antagonist… [that] is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based

chimeric molecules." Ex.1001, 2:51-56. The specification of the '572 patent states that the term "aflibercept" and "VEGFR1R2-FcΔC1(a)" are two terms that refer to the same "exemplary VEGF antagonist." *Id.* The Examples in the '572 patent describe the same clinical trials described in NCT-795 and NCT-377, using aflibercept (referred to in the examples as VEGFT). Ex.1001, Example 4, and 5:23-26. These are the same clinical trials that supported the FDA approval of aflibercept. Ex.1002, ¶185.

The last clause of claim 1 relates to the efficacy achieved through the claimed dosage regimen. As discussed above in Section IX.C, this statement of intended result is not given patentable weight because it does not alter the active steps of the claimed method.

Even if the Board disagrees that this last element should not be given patentable weight, both NCT-795 and NCT-377 still anticipate. For the reasons discussed below, NCT-795 and NCT-377 inherently anticipate this element. Ex.1002, ¶187-189.

NCT-795 and NCT-377 disclosed the details of the Phase 3 trials and noted that the primary outcome will be the proportion of patients who maintain vision at week 52. Ex.1010, 9; Ex.1011, 6. Although final results of the Phase 3 clinical trial were not reported in the literature until after the priority date of the '572 patent, NCT-795 and NCT-377's disclosure of the trial protocol nevertheless anticipates the

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present claims. The caselaw is clear that "newly discovered results of known processes… are inherent." *In re Montgomery*, 677 F.3d at 1381; *also Verdegaal*, 814 F. 2d at 633.

NCT-795 and NCT-377 are enabling because each describe the claimed methods of treatment with sufficient detail such that a POSA would be able to carry out the claimed methods. Ex.1002, ¶189; *Impax Labs*, 468 F.3d at 1383. Based on NCT-795 and NCT-377's description of the aflibercept Phase 3 clinical trials, a POSA would have known how to administer, what dosing schedule to follow, and how much aflibercept to administer to a patient to treat angiogenic eye disorders. Ex.1002, ¶189. Accordingly, NCT-795 and NCT-377 each anticipate claim 1.

The following table (confirmed by Dr. Tanna (Ex.1002, ¶190), shows how NCT-795 and NCT-377 each disclose each and every element of claim 1:

Claim 1:	**NCT-795:**	**NCT-377:**
A method of treating an angiogenic eye disorder in a patient in need thereof,	"A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With [AMD]." Ex.1010, 3, 4.	"A Randomized, Double Masked, Active Controlled Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With [AMD]." Ex.1011, 3.
comprising sequentially administering to the patient by intravitreal	"Official Title: A Randomized, Double Masked, Active	"Official Title: A Randomized, Double Masked, Active

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injection a **single initial dose** of 2 mg of aflibercept, followed by one or more **secondary doses** of 2 mg of aflibercept, followed by one or more **tertiary doses** of 2 mg of aflibercept;	Controlled, Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD)." Ex.1010, 3. "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." Ex.1010, 8.	Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." Ex.1011, 3-4. "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year." Ex.1011, 6.
	In other words, an "initial dose" at day 0, "secondary doses" at weeks 4 and 8; and "tertiary doses" every 8 weeks beginning at week 16 (i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**).	
wherein each secondary dose is administered approximately **4 weeks** following the immediately preceding dose; and	*Id.*	*Id.*
wherein each tertiary dose is administered approximately **8 weeks** following the immediately preceding dose;	*Id.*	*Id.*

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wherein the patient achieves a gain in **visual acuity within 52 weeks** following the initial dose.	Not given patentable weight. See Section IX.C.

The analysis for independent **Claims 26 and 29** is nearly identical. First, the dosing regimen elements are the same, which NCT-795 and NCT-377 each anticipate for the reasons stated above. The only differences between claims 26 and 29 and claim 1 is the identification of the disease to be treated and the particular non-limiting endpoint of the treatment. As shown below, and at Ex.1002, ¶191, NCT-795 and NCT-377 similarly anticipates claims 26 and 29:

Claim 26:	NCT-795:	NCT-377:
26. A method of treating **age related macular degeneration** in a patient in need thereof…	"Official Title: A Randomized, Double Masked, Active Controlled, Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD)." Ex.1010, 3.	"Official Title: A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." Ex.1011, 3-4.
wherein the method is **as effective** in **achieving a gain** in **visual acuity** as monthly administration	Not given patentable weight. See Section IX.C. Alternatively, this claim element is inherently	

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of 0.5 mg of ranibizumab… at 52 weeks following the initial dose.	anticipated for the same reasons as in claim 1 above. *Bristol*, 246 F.3d at 1380. [14]	
Claim 29:	**NCT-795:**	**NCT-377:**
29. A method of treating **age-related macular degeneration** in a patient in need thereof…	"Official Title: A Randomized, Double Masked, Active Controlled, Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration (AMD)." Ex.1010, 3.	"Official Title: A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." Ex.1011, 3-4.
wherein the method is **as effective** in **maintaining visual acuity** as monthly administration of 0.5 mg of ranibizumab …at 52 weeks following the initial dose.	Not given patentable weight. See Section IX.C. Alternatively, this claim element is inherently anticipated for the same reasons as in claim 1 above.[15]	

[14] NCT-795 and NCT-377 teach that the Phase 3 trial is an "active controlled" study comparing aflibercept to ranibizumab as the "active comparator." Ex.1010, 3, 8; Ex.1011, 3, 6.

[15] NCT-795 and NCT-377 teach that the Phase 3 trial compared aflibercept to ranibizumab. Ex.1010, 3, 8; Ex.1011, 3, 6.

a. Dependent claims 2-5, 8-11, 14, 27, 28, and 30

Claims 5, 11, and 27 further limit the claimed dosing regimen as follows: "wherein only two secondary doses are administered to the patient"— i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. NCT-795 and NCT-377 disclose "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year," (Ex.1010, 8; Ex.1011, 6), *i.e.*, a single initial dose plus two secondary doses administered four weeks apart. Ex.1002, ¶192. Accordingly, NCT-795 and NCT-377 respectively disclose the additional limitations, and thus each anticipates.

Claims 2-4, 8-10, 28, and 30 are all directed to specific effects achieved by following the dosing method disclosed in the prior art. As described above in Section IX.C, none of these specific effects should be given patentable weight. Accordingly, NCT-795 and NCT-377 each anticipate these claims.

However, even if the Board gives the specific effects recited in these dependent claims patentable weight, NCT-795 and NCT-377 still inherently anticipate. Ex.1002, ¶194. While NCT-795 and NCT-377 did not disclose the final results of the Phase 3 trial showing the various efficacy claimed in claims 2, 3, 8, 10, 28, and 30, or the speed at which patients achieved this efficacy as claimed in claims 4 and 9, these disclosures still anticipate. *In re Montgomery*, 677 F.3d at 1382.

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Here, NCT-795 and NCT-377 teach the exact method of the claims, and use of the method for the identical purpose (*i.e.*, the use of aflibercept to treat angiogenic eye disorder). Ex.1002, ¶194.

Claim 14 specifies that the patients to be treated will exclude patients that have active ocular inflammation and active ocular or periocular infection. As noted above, the exclusion criteria are not entitled to patentable weight, and thus are unable to distinguish the claims from the prior art. Therefore, for the same reasons that claim 1 is anticipated, claim 14 is likewise anticipated.

Notwithstanding, NCT-795 and NCT-377's disclosure of the details surrounding the Phase 3 aflibercept trial inherently discloses these claim elements.

A POSA would know that the Phase 3 trial disclosed by NCT-795 and NCT-377 would necessarily exclude patients having active ocular inflammation or active ocular or periocular infection. Ex.1002, ¶197.

First, the ranibizumab trials excluded people with "[a]ctive intraocular inflammation (grade trace or above) in the study eye" and "[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye." Ex.1002, ¶198; Ex.1026, Supplemental Appendix; *also*, Ex.1019, 2.

Additionally, a POSA would understand that patients having active ocular inflammation or active ocular or periocular infection should be excluded from

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intravitreal injection treatment. Ex.1032, 76, 81, 85; Ex. 1002, ¶199. Moreover, it was known that intravitreal injections presented further complications for such patients. Ex.1006, 1577; Ex.1033, 677; Ex.1032, 67, 69, 74-75; Ex.1014, 2537; Ex.1002, ¶199.

As the aflibercept trial was set up as a non-inferiority study comparing the effectiveness of aflibercept to the effectiveness of ranibizumab, a POSA would know that in order to have a meaningful head-to-head statistical comparison one would need a very similar patient population in both trials. Ex.1002, ¶199. A clinical study designer/investigator would understand that the way to do this is to adopt the same, or very similar, inclusion/exclusion criteria as those used in the comparator study. *Id.*; *also* Ex.1014.[16] This understanding is confirmed by the FDA guidance on non-inferiority studies. Ex.1031, 15-16. Thus, a POSA would understand that the clinical trial disclosed in NCT-795 and NCT-377 necessarily excluded people with active intraocular inflammation or active eye infections. Ex.1002, ¶200.

Further, by the earliest filing date of the '572 patent, additional details regarding the Phase 3 trials were made public—informing a POSA of these additional details. Ex.1002, ¶201. For example, in Nguyen-2006, exclusion criteria for the Phase 3 trial are listed. One of the exclusion criteria is identified as

[16] Heier 2012 also confirms that the Phase 3 trial did, in fact, exclude such patients. Ex.1030 (Appendix 2).

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"[p]resence of a disease other than NVAMD in the study eye that could affect vision or safety assessments." Ex.1023, 3; Ex.1005, Table 1. A POSA would understand that the presence of active ocular inflammation and active ocular or periocular infection would be such a condition that "could affect vision or safety assessments." Ex.1002, ¶201. As discussed above, the presence of active inflammation or infection is contraindicated with treatment administered through intravitreal injection.

Thus, a POSA would understand that the clinical trial disclosed in NCT-795 and NCT-377 excluded the patients described in claim 14. Accordingly, NCT-795 and NCT-377 each anticipate claim 14.

* * *

Each anticipatory reference asserted herein is presumed enabling and it is Regeneron's burden to rebut those presumptions. *See, e.g.*, *In re Antor Media Corp.*, 689 F.3d 1282, 1287- 88 (Fed. Cir. 2012); *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 659- 60 (D. Del. 2014). Any attempted rebuttal here would be futile because each reference sets forth a clear method and dosing regimen that a skilled artisan would have no trouble following.

B. OBVIOUSNESS

As described below, claims 6, 7, 12, and 13 are obvious over either Dixon, Regeneron (8-May-2008), NCT-795, or NCT-377 in combination with Hecht.

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1. Ground 5: Claims 6, 7, 12, and 13 are obvious over Dixon, or Regeneron (8-May-2008), or NCT-795, or NCT-377 in combination with Hecht

Claims 6 and 10 require that the "aflibercept is formulated as an isotonic solution." Claims 7 and 13 require that the "aflibercept is formulated with a nonionic surfactant." Each of these claims would be obvious in view of the prior art teachings on ophthalmic preparations.

As discussed above, each of Dixon, Regeneron (8-May-2008), NCT-795, and NCT-377 discloses each and every element of the claims upon which claims 6, 7, 10, and 13 depend. The addition of the unremarkable limitations of using an isotonic formulation in the eye, and using a nonionic surfactant in the formulation would have been obvious to a POSA.

Dixon teaches that aflibercept is "formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye." Ex.1006, 1575. A POSA would understand that if a formulation was not isotonic, it would cause irritation in the patient when injected into the eye. Ex. 1002, ¶205. At a minimum, a POSA would know that the formulation should be isotonic—and in fact, the POSA would expect that the aflibercept formulation used in Dixon was isotonic. Hecht provides guidance on formulating ophthalmic solutions and teaches that ophthalmic solutions "are formulated to be sterile, isotonic and buffered for stability and comfort." Ex.1025,

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1569. Hecht further states that "[g]iven a choice, isotonicity always is desirable and particularly is important in intraocular solutions." *Id.* at 1571. A POSA would have been motivated formulate aflibercept as an isotonic solution so that it would be non-irritating when administered to a patient's eye, and would have had a reasonable expectation of success in doing so. Ex.1002, ¶205.

A POSA would have been further motivated to combine Dixon and Hecht to arrive at an aflibercept formulation that contains a nonionic surfactant. Ex.1002, ¶206. Hecht teaches that nonionic surfactants can be used in ophthalmic solutions because they are "least toxic to the ophthalmic tissues," and they can act "as aids in achieving solution clarity," or "as cosolvents to increase solubility." Ex.1025, 1571. Additionally, surfactants have long been known to aid in stabilizing a protein, such as aflibercept, in a formulation. Ex.1027, 159. The surfactants typically used as stabilizing agents are non-ionic. *Id.* at 161. A POSA would have been motivated to formulate aflibercept with a nonionic surfactant to achieve a clear solution, to increase solubility, and to enhance the protein stability. Ex.1002, ¶206. The POSA would have had a reasonable expectation of success in doing so, evidenced at least in that aflibercept was already successfully formulated with a non-ionic surfactant and administered to macaques through an intravenous injection. *Id.*; Ex.1028 at 1115.

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Accordingly, claims 6, 7, 10, and 13 are obvious over each of Dixon, Regeneron (8-May-2008), NCT-795, and NCT-377 in view of Hecht.

2. No secondary considerations

When relying on secondary considerations—including, e.g., long-felt need, unexpected results, commercial success—as evidence of non-obviousness, a patentee must establish a nexus between the secondary considerations and the claimed invention. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006). There is no nexus unless the offered secondary consideration actually results from something that is both claimed and novel in the challenged claim. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068, 1074 (Fed. Cir. 2011).

Petitioner is not aware of any secondary considerations that would support a finding of non-obviousness. Further, even if such secondary considerations exist, they are not applicable to the robust anticipation grounds presented herein, and they cannot overcome the strong *prima facie* case of obviousness discussed above. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

The claims discussed above are anticipated by the prior art. Only claims 6, 7, 10, and 13 are presented here for obviousness. Claims 6 and 10 require that the "aflibercept is formulated as an isotonic solution." Claims 7 and 13 require that the "aflibercept is formulated with a nonionic surfactant." Thus, Regeneron would have to establish a nexus between any secondary considerations and the presence of an

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isotonic solution or nonionic surfactant in the formulation. They will not be able to do so.

To the extent Regeneron argues long-felt but unmet need, it will be unable to establish a "need" for an isotonic formulation or for the use of a nonionic surfactant, or show that any such need was "long-felt" because these elements were already known in the prior art.

Should Regeneron argue that any purported commercial success of EYLEA® is pertinent to patentability, Regeneron will be unable to establish that such purported commercial success is attributable to the claimed isotonic formulation or the use of a nonionic surfactant.

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

XIII. CONCLUSION

The Challenged Claims are unpatentable in view of the prior art as set forth in the Grounds asserted herein. Petitioner therefore requests that trial be instituted and the Challenged Claims cancelled.

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Dated: September 9, 2022

Respectfully Submitted,

/Teresa Stanek Rea/

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing Petitioner Apotex Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 11,253,572, and Exhibits 1001-1058, were served on September 9, 2022, via FedEx Priority Overnight on the Patent Owner at the correspondence address of record for U.S. Patent No. 11,253,572 as evidenced in Public Pair:

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/Shannon Lentz/
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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,998 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a).

Dated: September 9, 2022

/Shannon Lentz/
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