UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI SWISSBIOSIM GMBH,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Case No. 2025-01269
U.S. Patent No. 10,828,345 B2

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,828,345 B2

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EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 10,828,345 B2 ("the '345 patent")
1002	File History of U.S. Patent No. 10,828,345 B2
1003	Expert Declaration of Dr. John C. Galanis in Support of Petition for Inter Partes Review of Patent No. 10,828,345 B2 ("Galanis Report")
1004	Curriculum Vitae of Dr. John C. Galanis
1005	Jocelyn Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 PROC. NAT'L ACAD. SCI. 11393 (2002) ("Holash")
1006	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")
1007	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")
1008	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")
1009	U.S. Patent No. 9,254,338 B2 ("the '338 patent")
1010	U.S. Patent No. 7,531,173 B2 ("the '173 patent")
1011	U.S. Patent No. 7,396,664 B2 ("the '664 patent")
1012	U.S. Patent No. 7,374,758 B2 ("the '758 patent")
1013	U.S. Patent No. 10,888,601 B2 ("the '601 patent")
1014	IPR2022-01226, *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.,* Final Written Decision for U.S. Patent No. 10,888,601 (Jan. 9, 2024) ("FWD IPR2022-01226")
1015	IPR2021-00881, *Mylan Pharmaceuticals Inc., et al. v. Regeneron Pharmaceuticals, Inc.,* Final Written Decision for U.S. Patent No. 9,254,338 (Nov. 9, 2022) ("FWD IPR2022-00881")
1016	Jeffery S. Heier, *VEGF Trap-Eye for Exudative AMD*, RETINAL PHYSICIAN, Apr. 2009 ("Heier-2009")
1017	Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular

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	Degeneration (AMD) (VIEW 1), NCT00509795, ClinicalTrials.gov (Apr. 28, 2009), https://clinicaltrials.gov/ct2/show/NCT00509795 ("NCT-795")
1018	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")
1019	Regeneron. [Press Release] *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-releasedetails/positive-interim-phase-2-data-reported-vegf-trap-eye-agerelated?releaseid=394105 ("Regeneron (27-March-2007)")
1020	Regeneron. [Press Release] *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-releasedetails/regeneron-and-bayer-healthcare-initiate-phase-3-global ("Regeneron (2-Aug-2007)")
1021	Regeneron. [Press Release] *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-Apr-2008)")
1022	Regeneron. [Press Release] *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 (2008-May-08)")
1023	Regeneron. [Press Release] *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-releasedetails/regeneron-and-bayer-healthcare-announce-vegf-trap-eyeachieved?ReleaseID=394056 ("Regeneron (19-August-2008)")

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1024	Patrick S. Sharp, *The Role of Growth Factors in the Development of Diabetic Retinopathy,* 44 METABOLISM No. 10, Suppl. 4, 72-75 (Oct. 1995) ("Sharp")
1025	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")
1026	Talia N. Crawford, et al., *Diabetic Retinopathy and Angiogenisis*, 5 Current Diabetes Reviews, 8-13 (2009) ("Crawford")
1027	Napoleone Ferrara & Robert S. Kerbel, *Angiogenesis as a Therapeutic Target*, 438 NATURE 967 (2005) ("Ferrara-2005")
1028	Ziad F. Bashshur et al., *Intravitreal Bevacizumab for the Management of Choroidal Neovascularization in Age-Related Macular Degeneration*, 142 AM. J. OPHTHALMOLOGY 1 (2006) ("Bashshur")
1029	LUCENTIS® Prescribing Information (2006) ("Lucentis")
1030	RESERVED
1031	Jeffrey S. Heier et al., *Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration*, 119 OPHTHALMOLOGY 2537 (2012) ("Heier-2012")
1032	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")
1033	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")
1034	John S. Rudge et al., *VEGF Trap Complex Formation Measures Production Rates of VEGF, Providing a Biomarker for Predicting Efficacious Angiogenic Blockade*, 104 PNAS 18363 (2007) ("Rudge-2007")
1035	John S. Rudge et al., *Clinical Development of VEGF Trap*, ANGIOGENESIS, Chpt. 36 (William D. Figg & Judah Folkman eds. 2008) ("Rudge-2008")

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1036	Candelaria Gomez-Manzano et al., *VEGF Trap Induces Antiglioma Effect at Different Stages of Disease*, 10 NEURO-ONCOLOGY 940 (2008) ("Gomez-Manzano")
1037	Regeneron Pharm., Inc., Quarterly Report (Form 10-Q) (Sept. 30, 2009) ("2009 10-Q")
1038	P Mitchell et al., *Ranibizumab (Lucentis) in Neovascular Age-Related Macular Degeneration: Evidence from Clinical Trials*, 94 BRIT. J. OPHTHALMOLOGY 2 (2009) (date of online publication) ("Mitchell")
1039	Regeneron. [Press Release] *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/newsreleases/news-release-details/vegf-trap-eye-final-phase-2-resultsage-related-macular?ReleaseID=393906 ("Regeneron (28-September-2008)")
1040	Regeneron. [Press Release] *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/newsrelease-details/enrollment-completed-regeneron-and-bayerhealthcare-phase-3?ReleaseID=408872 ("Regeneron (14-September-2009)")
1041	Napoleone Ferrara et al., *Development of Ranibizumab, and Anti-Vascular Endothelial Growth Factor Antigen Binding Fragment, as Therapy for Neovascular Age-Related Macular Degeneration*, 26 RETINA, THE J. OF RETINAL AND VIDTREOUS DISEASES, No. 8, 859-870 (2006) ("Ferrara-2006")
1042	Heinrich Heimann, *Intravitreal Injections: Techniques and Sequelae*, MEDICAL RETINA 67 (Frank G. Holtz & Richard F. Spaide eds. 2007) ("Heimann-2007")
1043	U.S. Application Publication No. 2007/0190058 ("the '058 application")
1044	Pascale Massin, et al., *Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study),* 33 DIABETES CARE, No. 11 (Nov. 2010) ("Massin")

Exhibit	Description
1045	Anne F. Fung, et al., *An Optical Coherence Tomography-Guided, Variable Dosing Regimen with Intravitreal Ranibizumab (Lucentis) for Neovascular Age-related Macular Degeneration,* AM. J. OPTHAMOLOGY 143:566-583 (Apr. 2007) ("Fung")
1046	IPR2022-01225, *Mylan Pharmaceuticals Inc., v. Regeneron Pharmaceuticals, Inc,* Final Written Decision for U.S. Patent No. 10,130,681 (Jan. 9, 2024) ("FWD IPR2022-01225")
1047	U.S. Patent No. 10,888,601, Disclaimer in Patent Under 37 CFR. 1.321(a), dated July 10, 2024
1048	U.S. Patent No. 11,253,572, Disclaimer in Patent Under 37 CFR 1.321(a) dated July 10, 2024
1049	File History of U.S. Patent No. 7,374,758 ("758 FH")
1050	File History of U.S. Patent No. 7,070,959 ("959 FH")
1051	File History of U.S. Patent No. 10,130,681 ("681 FH")
1052	Regeneron. [Press Release] *VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients with Diabetic Macular Edema* (Feb. 18, 2010), https://investor.regeneron.com/news-releases/news-release-details/vegf-trap-eye-shows-positive-results-phase-2-study-patients ("Regeneron (18-Feb-2010)")
1053	"History, Policy, and Laws", clinicaltrials.gov (Apr. 26, 2021) https://clinicaltrials.gov/ct2/about-site/history
1054	EYLEA® Prescribing Information
1055	EYLEA HD® Prescribing Information

Fresenius Kabi SwissBioSim GmbH ("Fresenius" or "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 1-11 (the "Challenged Claims") of U.S. Patent No. 10,828,345 ("the '345 patent") (Ex. 1001), assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

I. INTRODUCTION

The Challenged Claims are invalid for anticipation and/or obviousness, and should never have issued. They are drawn to "VEGF antagonist," including VEGF Trap-Eye/aflibercept dosing and administration regimens for treating angiogenic eye disorders, including age-related macular degeneration ("AMD") and diabetic retinopathy. The methods recited in the Challenged Claims were known to persons of ordinary skill in the art ("POSA") pursuant to prior art references and a POSA's knowledge before the alleged 2011 priority date.

VEGF Trap-Eye—*i.e.*, aflibercept—was a known blocker of vascular endothelial growth factor ("VEGF") independently disclosed in the scientific literature, (Ex. 1035; Ex. 1016; Ex. 1006; Ex. 1007; Ex. 1008) and patented (Ex. 1010; Ex. 1011; Ex. 1012) well before the alleged priority date.

Regeneron also publicly disclosed the claimed dosing and administration regimens as early as 2008, three years prior to filing its patent application. Ex. 1003,

at ¶¶ 62, 135, 142, 185-86, and 285; Ex. 1017; Ex. 1018; Ex. 1022. In fact, the PTAB—resolving IPRs for patents claiming inventions similar or the same as those recited in the Challenged Claims—has also previously held that the prior art disclosed clinical trials (VIEW 1/VIEW 2) in which the claimed active pharmaceutical ingredient (VEGF antagonist/aflibercept) was administered according to the claimed dosage and administration regimens. *See, e.g.,* Ex. 1014, Ex. 1015. For similar reasons, the Challenged Claims at issue here are also unpatentable. Accordingly, there exists a reasonable likelihood that Petitioner will prevail in demonstrating unpatentability of at least one of the Challenged Claims.

Petitioner thus filed this Petition, supported by an expert declaration from Dr. John C. Galanis. Ex. 1003.

Anticipation. Each claim 1-9 of the '345 patent are anticipated. Regeneron and others published several references that disclosed at least two clinical trials—i.e., VIEW 1 and VIEW 2—involving the administration of aflibercept for the treatment of an angiogenic eye disorder using the claimed dosing and administration regimens. Ex. 1003 at ¶¶ 62, 128, 137, and 184; Ex. 1017; Ex. 1018; Ex. 1022. These publications disclosed *all* of the elements of the methods recited in claims 1-9 of the '345 patent—including administering an initial, secondary, and tertiary dose,

wherein the tertiary dose is administered 12 weeks after the immediately preceding dose.

Obviousness. The claimed methods for the treatment of diabetic retinopathy and DME would have been obvious to a POSA as of the alleged priority date of the '345 patent. This is particularly the case in view of Regeneron's prior art disclosure of positive 0.5 mg and 2.0 mg VEGF Trap-Eye/aflibercept data from a Phase 2 study for the treatment of DME. Ex. 1052 at 1. In fact, POSAs even commented that the data showed VEGF Trap-Eye/aflibercept "significantly improve[s] vision in patients with DME[.]" *Id*.

Moreover, a POSA would have been motivated to apply the dosing regimen disclosed by Regeneron for the treatment of diabetic retinopathy, including diabetic macular edema (DME) because (i) AMD and diabetic retinopathy share the same pathogenesis; (ii) VEGF Trap-Eye/aflibercept targets the shared pathogenesis; (iii) there was a desire to reduce the frequency of intravitreal injections in the treatment of diabetic retinopathy; and (iv) VEGF Trap-Eye/aflibercept had been shown to be effective in treated diabetic retinopathy from less frequent administrations. Ex. 1003 at ¶¶ 244, 312, and 315.

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)).

The real parties-in-interest are Fresenius Kabi USA, LLC, Fresenius Kabi SwissBioSim GmbH, Fresenius Kabi AG. Another party-in-interest is Sam Chun Dang Pharm Co., Ltd.

B. Related Matters (37 C.F.R. § 42.8(b)(2)).

Petitioner identifies the following consolidated IPR proceedings, pursuant to which the PTAB issued a final determination (Ex. 1015) in which it determined that claims 1, 3-11, 13, 14, 16-24 and 26 of U.S. Patent No. 9,254,338 ("the '338 patent") are unpatentable:

- *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2021-00881;
- *Celltrion Inc. et al. v. Regeneron Pharmaceuticals, Inc.*, IPR 2022-00298; and
- *Apotex, Inc. et al. v. Regeneron Pharmaceuticals, Inc.,* IPR 2022-00258.

Further, Petitioner identifies the following consolidated IPR proceedings, pursuant to which the PTAB issued a final determination (Ex. 1046), FWD IPR in

which it determined that claims 1, 3-11, 13, 14, 16-24 and 26 of U.S. Patent No. 10,130,681 ("the '681 patent") are unpatentable:

- *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2022-01225; and
- *Celltrion Inc et al. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00532;
- *Samsung Bioepsis Co. Ltd. v. Regeneron Pharmaceuticals, Inc.,* IPR2023-00442.

Further, Petitioner identifies the following consolidated IPR proceedings, pursuant to which the PTAB issued a final determination (Ex. 1014) in which it determined that claims 1-9, 34-39, 41-43 and 45 of the '601 patent are unpatentable:

- *Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.,* IPR2022-01226;
- *Celltrion, Inc. et al. v. Regeneron Pharmaceuticals., Inc.*, IPR2023-00533; and
- *Samsung Bioepis Co., Ltd. v. Regeneron Pharmaceuticals., Inc*., IPR2023-00566.

Further, Petitioner identifies the following consolidated IPR proceedings, for which the PTAB did not issue a final written decision because the Patent Owner filed Disclaimers under 37 C.F.R. § 1.321(a) disclaiming claims 10-33 and 46-47 of the '601 patent (Ex. 1047):

- *Samsung Bioepsis Co., Ltd., et al. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00739; and

- *Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc.,* IPR2024-00201.

Further, Petitioner identifies the following consolidated IPR proceedings, for which the PTAB did not issue any final written decision because Patent Owner filed a Disclaimer under 37 C.F.R. § 1.321(a), disclaiming claims 1-30 in U.S. Patent No. 11,253,572 ("the '572 patent") (Ex. 1048):

- *Samsung Bioepsis Co., Ltd., et al. v. Regeneron Pharmaceuticals, Inc.*, IPR2023-00884;

- *Celltrion, Inc. v. Regeneron Pharmaceuticals, Inc.*, IPR2024-00260; and

- *Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc.,* IPR2024-00298.

Additionally, Petitioner identifies *Chengdu Kanghong Biotechnology Co. v. Regeneron Pharms., Inc.*, PGR2021-00035 (PTAB) (proceeding terminated before institution) as a related matter.

Finally, Petitioner identifies the following district court litigations as related matters:

- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis, Inc.*, No. 1:23-cv-00094 (N.D. W.Va.);

- *Regeneron Pharmaceuticals, Inc. v. Samsung Bioepis, Inc.*, No. 1:23-cv-00106 (N.D. W.Va.);

- *Regeneron Pharmaceuticals, Inc. v. Formycon*, No. 1:23-cv-00097 (N.D. W.Va.);

- *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 1:22-cv-00061-TSK (N.D. W.Va.); and

- *Regeneron Pharmaceuticals, Inc. v. Celltrion, Inc.*, No. 1:23-CV-0089 (N.D. W.Va).

C. Lead and Back-Up Counsel (37 C.F.R. § 4,8(b)(3)-(4))

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

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

This Petition is being served by Federal Express Next Business Day Delivery to the correspondence address of record for the '345 patent:

191459 - A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743

The Petition is further being served on Litigation Counsel for Regeneron Pharmaceuticals, Inc. by electronic mail at: dberl@wc.com.

Please direct all correspondence to lead and back-up counsel at the contact information above. Petitioner also consents to service by email at: AFS-Fresenius-aflibercept345IPR@afslaw.com. Petitioner intends to file a motion seeking the admission of Ahmed M.T. Riaz to appear *pro hac vice* when authorized to do so.

E. Power of Attorney (§ 41.20(b))

Petitioners' Power of Attorney forms will be filed concurrently herewith in accordance with 37 C.F.R § 41.10(b).

III. PAYMENT OF FEES (37 C.F.R. §§ 42.103 AND 42.15(A))

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. 506990.

IV. GROUNDS FOR STANDING (37 C.F.R. § 42.104(A); 37 C.F.R. §§ 42.101(A)-(C))

Petitioner certifies that the '345 patent—which allegedly claims priority to 2011 and was issued on November 10, 2020—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 validity, or been served with a complaint alleging infringement, of the '345 patent, more than one year prior to the filing of this Petition. *See Motorola Mobility LLC v. Arnouse,* No. IPR2023-00010, 2013 WL 12349001, *3 (P.T.A.B. Jan. 23, 2013).

V. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW.

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

unpatentable claims recited in patents of the same family as the ’345 patent and which are substantively similar or the same as the Challenged Claims.

VI. IDENTIFICATION OF CHALLENGE AND RELIEF REQUESTED

A. Identification of Challenge (37 C.F.R. § 42.104(b))

Petitioner respectfully requests IPR of ’345 patent claims 1-11 and that the PTAB cancel those claims as unpatentable.

B. Grounds of Challenge (37 C.F.R. § 42.204(b)(2))

Petitioner respectfully requests that the PTAB grant institution of IPR on the Challenged Claims based on the following grounds:

STATUTORY GROUNDS OF CHALLENGE	
GROUND 1 (35 U.S.C. § 102)	Claims 1-9 of the ’345 patent are anticipated by Dixon
GROUND 2 (35 U.S.C. § 102)	Claims 1-9 of the ’345 patent are anticipated by NCT-377
GROUND 3 (35 U.S.C. § 102)	Claims 1-9 of the ’345 patent are anticipated by NCT-795
GROUND 4 (35 U.S.C. § 102)	Claims 1-9 of the ’345 patent are anticipated by Regeneron (8-May-2008)
GROUND 5 (35 U.S.C. § 103)	Claims 1-9 of the ’345 patent are obvious over Dixon in view of NCT-377
GROUND 6 (35 U.S.C. § 103)	Claims 10 and 11 of the ’345 patent are obvious over NCT-795 in view of Regeneron (18-Feb-2010) and a POSA’s knowledge
GROUND 7 (35 U.S.C. § 103)	Claims 10 and 11 of the ’345 patent are obvious over NCT-377 I view of Regeneron (18-Feb-2010) and a POSA’s knowledge
GROUND 8 (35 U.S.C. § 103)	Claims 10 and 11 of the ’345 patent are obvious over Dixon in view of Regeneron (18-Feb-2010)
GROUND 9 35 U.S.C. § 103)	Claims 10 and 11 of the ’345 patent are obvious over Regeneron (8-May-2008) in view of Regeneron (18-Feb-2010), and a POSA’s knowledge

Petitioner’s full statement of reasons for the relief requested is set forth in greater detail below, and in the supporting declaration of Dr. John C. Galanis (Ex. 1003).

VII. THE '345 PATENT[1]

A. Overview

The '345 patent, titled "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders" was issued November 10, 2020 from U.S. Patent Application Number 16/159,282 ("the '282 application"). On its face, the '345 patent indicates it is currently assigned to Regeneron Pharmaceuticals, Inc., and names George D. Yancopoulos as the sole inventor.

The '345 patent specification discloses that "the methods of the invention comprise sequentially administering multiple doses of a VEGF antagonist" to treat angiogenic eye disorders, i.e., eye disorders caused by or associated with the formation of new blood vessels. Ex. 1001, 2:4-6.

The '345 patent also provides "background" information regarding the state of the art as of the alleged priority date. Specifically, it confirms that "[s]everal eye disorders are associated with pathological angiogenesis" including AMD and DME, which "is another eye disorder with an angiogenic component." Ex. 1001 at 1:31-33; 1:37-38. The background section also explains that DME "is a common complication of diabetic retinopathy, a disease affecting the blood vessels of the

[1] For purposes of this petition only, Petitioner assumes a priority date of January 21, 2011. However, Petitioner reserves all rights to challenge this priority date, including to the extent to which Regeneron asserts application of pre-AIA standards of patentability.

retina" and that "[c]linically significant DME occurs when fluid leaks into the center of the macula[.]" *Id.* at 1:39-44. The background section goes on to acknowledge that "[r]elease of [VEGF] contributes to increased vascular permeability in the eye and inappropriate new vessel growth. Thus, inhibiting the angiogenic promoting properties of VEGF appears to be an effective strategy for treating angiogenic eye disorders." *Id.* at 1:51-56.

Further, while there were VEGF-inhibitors available on the market as of the alleged priority dates, the background section of the '345 patent explains that these drugs required administration "on a monthly basis by intravitreal injection." *Id.* at 1:57-60. In fact, prior to 2011, ranibizumab (LUCENTIS®) and Bevacizumab (AVASTIN®), which are anti-VEGF antibody drug products were administered to treat eye disorders pursuant to extended dosing regimens. Ranibizumab, which was FDA-approved for monthly administration via intravitreal injunction to treat AMD, (Ex. 1029, Lucentis at 1), was typically administered on a *pro re nata* (p.r.n.) or "as needed" basis. Bevacizumab (AVASTIN®) was extensively used off-label to treat angiogenic eye disorders. Ex. 1007 at 2. This drug was often administered as needed. Ex. 1028 at 8.

The background also acknowledges that there were "[m]ethods for treating eye disorders using VEGF antagonists [that] are mentioned in e.g., U.S. Pat. Nos.

7,303,746; 7,306,799; 7,300,563; 7,303,748; and US 2007/0190058" but that "there remains a need in the art for new administration regimes for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy." Ex. 1001 at 1:61-67.

Examples 1-6 of the '345 patent describe the results of Phase I, II, or III clinical trials using different dosing regimens of "VEGF Receptor-Based Chimeric Molecule (VEGFT)" in subjects with AMD (Examples 1-4), DME (Example 5), or macular edema secondary to central retail vein occlusion (CRVO) (Example 6). *Id.* at Cols. 8-15. Example 7 of the '345 patent describes additional dosing regimens, but does not contain any test results. *Id.* at 15:36-17:8. Notably, the specification does not disclose that VEGFT was administered 12 weeks after the immediately preceding dose for the treatment of DME in any subjects. Thus, there is no data disclosed in the '345 patent for the administration of a VEGF antagonist for the treatment of diabetic retinopathy or DME according to the method recited in claims 10 or 11.

B. The Challenged Claims

The '345 patent issued with 11 claims of which claim 1 is independent. The claims of the '345 patent are directed to methods for treating an angiogenic eye disorder in a patient by administration of a "single initial dose" of "a VEGF

antagonist," including VEGF Trap-Eye/aflibercept, followed by secondary doses each of which "is administered 4 weeks after the immediately preceding dose" followed by one or more tertiary doses each of which "is administered 12 weeks after the immediately preceding dose." Ex. 1001 at Claim 1. Claims 10 and 11 recite the dosing schedule wherein the angiogenic eye disorder is diabetic retinopathy (claim 10) and DME (claim 11).

C. Prosecution History

The '345 patent issued from U.S. Application No. 16/159,282 ("the '282 application"), filed October 12, 2018. Ex. 1001. During prosecution, the Examiner issued a non-final office action rejecting all pending claims on grounds of non-statutory obviousness-type double patenting over claims 1-5 of U.S. Patent No. 7,303,746 ("the '746 patent"), claims 1-6 of U.S. Patent No. 7,303,747 ("the '747 patent"), claims 1-11 of U.S. Patent No. 7,306,799 ("the '799 patent"), claims 1-15 of U.S. Patent No. 7,521,049 ("the '049 patent"), claims 1-26 of U.S. Patent No. 9,254,338 ("the '338 patent"), claims 1-12 of U.S. Patent No. 9,669,069 ("the '069 patent"), and claims 1-12 of U.S. Patent No. 10,130,681 ("the '681 patent"). Ex. 1002 at 338-346, Apr. 3, 2019 Office Action. The Examiner noted that though some of the double patenting references "d[o] not disclose the dosing schedules set forth in the instant claims, it is routine experimentation to optimize dosage and dosage

schedules." *Id.* at 341-45. The Examiner also noted that SEQ ID NO:16 disclosed in the '746 patent; SEQ ID NO:6 disclosed in the '747 and '799 patents; SEQ ID NO:23 disclosed in the '049 patent; and SEQ ID NO:2 disclosed in the '338, '681 and '069 patents "comprises an immunoglobin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor and a multimerizing component." *Id.* at 341-344. In response, the applicants submitted terminal disclaimers to the double patenting references. Ex. 1002 at 299, June 28, 2019 Resp. to Office Action.

Thereafter, the Examiner issued another non-final action rejecting pending claims 21-31 as anticipated by Dixon:

> Dixon et al. teaches methods for treating an angiogenic eye disorder, including age-related macular degeneration, diabetic retinopathy, and diabetic macular edema (See §2.6.1 and 2.6.2 at pp. 3-4) with the VEGF antagonist aflibercept. Dixon et al. teaches that patients received intraocular/intravitreal monthly doses of 0.5mg or 2mg for 12 weeks (0, 4, 8, 12) followed by treatment of the same dose on a PRN basis. Therefore, Dixon et al. teaches a treatment protocol of (1) a single dose of 0.5mg or 2mg at week 0, followed by 3 secondary doses in 4-week intervals (week 4, 8 and 12); followed by tertiary doses on a PRN basis. Dixon et al. further teaches criteria for PRN basis, including visual (ETDRS letters) or anatomical (retinal thickness by OCT) outcomes (See §2.6.2 at pg. 4). The VEGF antagonist disclosed by Dixon et al. is aflibercept, a VEGF trap which comprises immunoglobin-like (lg) domain 2 of Fltl, lg domain of 3 Flkl, and lgG Fe fragment

> as a multimerizing component (See §2.2 and §2.3 at pg. 3).

Ex. 1002 at 242-243, Oct. 1, 2019 Office Action. The Examiner also rejected pending claims 32-42 as anticipated by Regeneron 2009:

> Regeneron teaches methods for treating an angiogenic eye disorder, including neovascular age-related macular degeneration with the VEGF antagonist VEGF-Trap-Eye. Regeneron also teaches VEGF Trap Eye for the treatment of diabetic macular edema and central retinal vein occlusion (See pg. 1). Regeneron teaches that patients received intraocular/intravitreal doses of 0.5mg or 2g VEGF Tap-Eye at 4-week intervals in the first year, followed by continual treatment for another year on a flexible, PRN regiment, with a dose administered at least every 12 weeks, but not more often that every 4 weeks. Therefore, Regeneron teaches treatment of AMD patients with (1) a single dose of 0.5mg or 2mg, followed by (2) secondary doses at 4-week intervals for a year, followed by (3) treatment for another year based on a flexible PRN schedule, which would include at least one tertiary dose at 12 weeks from the immediately preceding dose. The VEGF antagonist disclosed by Regeneron is VEGF Trap-Eye, which is a VEGF trap which is a VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor. As disclosed in Dixon et al. (referenced *supra),* VEGF Trap Eye comprises immunoglobin-like (IG) domain 2 of Fltl, lg domain 3 of Flkl, and IgG Fe fragment as a multimerizing component (See §2.2 and §2.3 at pg. 3).

Id. at 243-44.

Thereafter, the applicant cancelled pending claims 21-32 (Ex. 1002 at 193, Mar. 16, 2020 Resp. to Office Action) and asserted that "[t]hough [Regeneron 2009]

discussed PRN dosing regimen wherein a dose interval may extend out as far as 12 weeks, the dosages administered to patients were not necessarily this infrequent." Ex. 1002 at 233, Jan. 23, 2020 Resp. to Office Action (emphasis in original).

During an Examiner Interview, "the Examiner requested further clarification … with respect to [Regeneron 2009] having an indicated date of September 14, 2009." *Id*. at 193. Thereafter, applicants argued that Regeneron 2009 had not been shown to be prior art even though it has a displayed date of September 14, 2009 and would have been published by Regeneron itself. *Id*. In July 2020, the Examiner issued a notice of allowance for the claims. Ex. 1002 at 24, July 22, 2020 Notice of Allowance.

In March 2022, applicant filed a Request for Certificate of Correction, correcting column 13, line 5; column 15, lines 9-10; and column 15, line 12 from "gained ≤15 ETDRS" to "gained ≥15 ETDRS". Ex. 1002 at 13, Mar. 4, 2022 Request for Cert of Correction.

D. Related Patents and IPR Decisions

As noted above in Section V of this Petition, the PTAB has already instituted IPR proceedings pursuant to which it has cancelled claims that are substantively similar to the claims recited in the '345 patent.

Particularly relevant to the present Petition, claims 1-9, 34-39, 41-43, and 45 of the ’601 patent were cancelled “as being anticipated by Dixon” pursuant to the PTAB’s Final Written Decision for consolidated IPR2022-01226; IPR2023-00533; IPR2023-00566. Ex. 1014 at 91. Dixon is the same as Ex. 1007 reference that forms the basis for several invalidity grounds in the present Petition.

Patent Owner also voluntarily filed a Disclaimer under 37 CFR 1.321(a) disclaiming claims 10-33 and 46-47, which had been the subject of PTAB instituted consolidated IPR2023-0073 and; IPR2024-00201. Ex. 1047. Importantly, claims 34-35, 37-43, and 46-47 of the ’601 patent are substantively similar to the claims 1-11 of the ’345 patent. In fact, the sole difference between the inventions recited independent claim 34 of the ’601 patent and claim 1 of the ’345 patent is with respect to the tertiary dose:

’601 Patent	**’345 Patent**
Claim 34 – A method for treating angiogenic eye disorder in a patient in need thereof, comprising	**Claim 1** – A method for treating an angiogenic eye disorder in a patient, said method comprising
Administering to the patient an effective sequential dosing regimen of a single initial dose of a VEGF antagonist,	sequentially administering to the patient a single initial dose of a VEGF antagonist,
Followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
Wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and	wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

’601 Patent	’345 Patent
Wherein each tertiary dose is **administered 8 weeks** after the immediately preceding dose;	wherein each tertiary dose is **administered 12 weeks** after the immediately preceding dose;
Wherein the VEGF antagonist is a receptor-based chimeric molecule comprising	wherein the VEGF antagonist is a receptor-based chimeric molecule comprising
An immunoglobin-like (1g) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second EGF receptor which is VEGFR2, and a multimerizing component.	an immunoglobin-like (lg) domain 2 of a first VEGF receptor which is Fltl and lg domain 3 of a second VEGF receptor which is Flkl, and a multimerizing component.
Claim 35 – The method of claim 34 wherein the VEGF antagonist is aflibercept.	**Claim 2** – The method of claim 1, wherein the VEGF antagonist is aflibercept.
Claim 37 – The method of claim 34, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.	**Claim 3** – The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
Claim 38 – The method of claim 37, wherein the intraocular administration is intravitreal administration.	**Claim 4** – The method of claim 3, wherein the intraocular administration is intravitreal administration.
Claim 39 – The method of claim 38, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.	**Claim 5** – The method of claim 4, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.
Claim 40 – The method of claim 39, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.	**Claim 6** – The method of claim 5, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.
Claim 41 – The method of claim 39, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.	**Claim 7** – The method of claim 5, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.
Claim 42 – The method of claim 34, wherein the angiogenic eye disorder is selected from the group consisting of:	**Claim 8 –** The method of claim 5, wherein the angiogenic eye disorder is selected from the group consisting of:

’601 Patent	’345 Patent
age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.	age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion and corneal neovascularization.
Claim 43 – The method of claim 34, wherein the angiogenic eye disorder is age related macular degeneration.	**Claim 9** – The method of claim 8, wherein the angiogenic eye disorder is age related macular degeneration.
Claim 46 – The method of claim 34, wherein the angiogenic eye disorder is diabetic retinopathy.	**Claim 10** – The method of claim 8, wherein the angiogenic eye disorder is diabetic retinopathy.
Claim 47 – The method of claim 34, wherein the angiogenic eye disorder is diabetic macular edema.	**Claim 11** – The method of claim 8, wherein the angiogenic eye disorder is diabetic macular edema.

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

A. “A method for treating an angiogenic disorder in a patient”

For purposes of this Petition only, Petitioner does not contest that the preamble of challenged claim 1 is limited, though it reserves the right to do so in separate proceedings.

B. “treating”

Petitioner proposes that the term “treating” be given the same meaning ascribed to that term by the PTAB in its Final Written Decision for related ’388 patent in IPR2021-0881. Importantly, the ’388 patent shares the same specification as the ’345 patent. In the IPR2021-00881 proceeding, the PTAB determined that “treating” should be given its plain and ordinary meaning, which is “administering a therapeutic to a patient, without a specific degree of efficacy required.” Ex. 1015

at 19. The PTAB rejected the Patent Owner's proposed construction—"a high level of efficacy, on par with the prevailing standard of care at the time of filing[]"—because it requires importing limitations into the claims. *Id.* at 19.

C. "initial dose", "secondary dose", "tertiary dose"

Petitioner proposes that the terms "initial dose", "secondary dose", and "tertiary dose" be given the same meaning ascribed to them by the PTAB in its Final Written Decision for the related '388 and '601 patents in IPR2022-0881 and IPR2022-01226, respectively. In those IPR proceedings, the PTAB determined that "initial dose", "secondary dose", and "tertiary dose" are expressly defined in the specification as follows:

> 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.

Ex. 1015 at 24-25, Ex. 1014 at 38, Ex. 1001 at 3:42-49.

IX. PERSON OF ORDINARY SKILL.

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.

Petitioner proposes the PTAB adapt the definition for a POSA that was adapted by the PTAB during the related IPR proceedings, including with respect to the '338 patent, '681 patent, '601 patent: A POSA at the time of the invention would have had (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. 1015 at 9-10; Ex. 1046 at 52-53; Ex. 1014 at 69.

X. TECHNOLOGY BACKGROUND

A. VEGF Trap-Eye/Aflibercept 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 IgG1. (*See* Ex. 1007 at 4, Fig. 1; Ex. 1021 at 2; Ex. 1005 at 2 (Fig.1A)). The terms aflibercept and VEGF Trap-Eye were

known in the art to refer to the same active ingredient. (Ex. 1007 at 1 ("***One*** promising new drug is aflibercept (VEGF Trap-Eye), ***a*** fusion protein...." (emphasis added)), *id.* at 3 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure"); Ex. 1008 at 1 ("Aflibercept...VEGF Trap-Eye"; "Aflibercept is in clinical development … for the treatment of cancer, while Regeneron and Bayer are developing the agent for eye disorders."), *id.* at 3 ("The VIEW2 trial...will evaluate the safety and efficacy of aflibercept"); Ex. 1003 at ¶ 179).

These prior art disclosures are consistent with Regeneron's later confirmatory statements to the Patent Office that (1) aflibercept and VEGF Trap-Eye were synonymous; (2) the construction of VEGF Trap-Eye/aflibercept was described in Holash (Ex. 1005); and (3) the sequence and domain composition of VEGF Trap-Eye/aflibercept was set forth in Regeneron's prior art '758 and '959 patents. Ex. 1049 at 2, 6-7; Ex. 1050 at 2, 5-7 ("The nucleic acid and amino acid sequence of $VEGF_{R1R2}$-FcΔC1(a) is provided in Figures 24A-C...[t]hus aflibercept is a fusion protein encoded by a nucleic acid sequence of SEQ ID NO: 15."; "aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-$TRAP_{R1R2}$")). Regeneron also represented to the Patent Office during prosecution of related patents that the VIEW clinical trials correspond to Example 4 in the specification—in other

words, the same trials, and the same molecule, disclosed in Petitioner's art (*e.g.*, Dixon, etc.) and later claimed in the '601 patent. *See, e.g.*, Ex. 1051 at 177 (June 25, 2018 Remarks).

Numerous prior art publications discussing both aflibercept and VEGF Trap-Eye cite back to Holash's disclosure of VEGF-Trap$_{R1R2}$. (Ex. 1034 at 1, 8 ("aflibercept" included as a keyword, citing back to Holash (ref. 11)); Ex. 1016 at 3 (discussing VEGF Trap-Eye and citing back to Holash, and discussing the data presented therein for VEGF Trap$_{R1R2}$); Ex. 1036 at 1, 6 ("a new anti-VEGF agent, VEGF Trap/aflibercept (henceforth referred to as VEGF Trap)," citing Holash).

Regeneron's patents confirm the identity of VEGF Trap-Eye/aflibercept. For example, Regeneron's prior art '173 patent discloses that "[i]n a ***specific and preferred embodiment, the VEGF trap is VEGF$_{R1R2}$-FcΔC1(a) (also termed VEGF trap$_{R1R2}$)***" and discloses a specific sequence. (Ex. 1010 at 1:48-52 (emphasis added)). Interested POSAs would have readily identified VEGF$_{R1R2}$-FcΔC1(a) as having the specific sequence disclosed for it in the '173 patent, and, based on a simple alignment, would have understood it to have the same sequence as aflibercept. A POSA further would have understood the VEGF Trap$_{R1R2}$ nomenclature to reference the single agent constructed and tested in Holash, and referenced in the numerous VEGF Trap-Eye/aflibercept references, including but not limited to those discussed

above, thus tying the sequences with the nomenclature, and confirming without a doubt, the identity and sequence of VEGF Trap-Eye/aflibercept.

B. ANTI-VEGF Therapy

As of 2011, POSAs knew that VEGF antagonists were useful in the treatment for patients with AMD and diabetic retinopathy, including DME. Ex. 1003 at ¶ 245; *see also, e.g.,* Ex. 1026, at 1. In fact, VEGF antagonists were being used and/or studied to treat angiogenic eye disorders, including AMD, diabetic retinopathy and diabetic macular edema. Ex. 1003 at ¶ 246; *see also, e.g.,* Ex. 1043 at Claim 21; Ex. 1007 at 2.

VEGF-agonist agents were already approved and being used (in some cases off-label) in the treatment of AMD, DME and RVO. Ex. 1003 at ¶ 50. Ranibizumab (LUCENTIS®) was approved for monthly dosing but was often being used on a p.r.n. basis. Ex. 1007 at 2. Bevacizumab (AVASTIN®) was approved for cancer indications but being used off-label to treat AMD. *Id*. At the time, ranibizumab approved indications, and the bevacizumab off-label use, overlapped those Regeneron was exploring for EYLEA®. Both ranibizumab and bevacizumab, like aflibercept, are VEGF antagonists.

However, among VEGF antagonists, VEGF Trap-Eye/aflibercept was recognized as "represent[]ing] the most promising anti-VEGF" drug that had

undergone Phase III trials." *Id.* at 5; *see also*, Ex. 1003 at ¶ 155. It was also recognized that "[i]n contrast to current anti-VEGF antibodies, which are rapidly cleared, the VEGF-VEGF Trap complex is relatively inert, and is degraded more slowly. Due to its high binding affinity and the ability to safely inject high doses into the eye, VEGF Trap-Eye may have longer duration of effect in the eye." *Id.*

Thus, before the alleged priority date, VEGF Trap-Eye was developed to target angiogenic disorders, including eye disorders, such as AMD, DME, and RVO. Regeneron placed VEGF Trap-Eye/aflibercept into clinical studies in the mid-2000's. (Ex. 1006 at 7 (reporting from Phase 1 study that "a single intraocular injection . . . appears safe and well tolerated" and that there were "substantial effects after single injections of 1.0 to 4.0 mg")).

In 2008, Regeneron publicly announced the results of its Phase 2 trial, CLEAR-IT-2, assessing p.r.n. dosing after 4 monthly loading doses for treatment of AMD. (Ex. 1021; Ex. 1022). Regeneron also announced initiation of its Phase 3 VIEW clinical trials for the treatment of AMD, (*Id.*), the same clinical trials discussed in Dixon and Adis. Ex. 1007; Ex. 1008. Regeneron provided detailed dosing information about the VIEW clinical trials on the clinicaltrials.gov website, where it registered. Ex. 1017 at 6, 7; Ex. 1018 at 8-9. The publicly disclosed prior art dosing regimen of the VIEW clinical trials disclosed by Regeneron in its

registration of the VIEW studies on the clinicaltrials.gov website is the same dosing regimen Regeneron claims in the '345 patent.

At least as early as 2008, Regeneron itself had disclosed that VEGF-antagonists including VEGF Trap-Eye/aflibercept "may be useful in treating clinical conditions that are characterized by vascular permeability, edema, or inflammation such as … diabetic retinopathy." Ex. 1012 at 15:61-16:6. Positive results from a VEGF Trap-Eye/aflibercept safety study for the treatment of DME were also disclosed. Ex. 1035 at 6; Ex. 1007 at 4.

In 2009, Regeneron and Bayer announced they were "conducting a Phase 2 study of VEGF Trap-Eye in patients with [DME]." Ex. 1037 at 19. And in 2010, Regeneron and Bayer announced that the Phase 2 study in patients with DME "showed positive results"; "[t]he ability of VEGF Trap-Eye to significantly improve vision in patients with DME in this initial Phase 2 study is encouraging"; and "The magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this Phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high level of vascular endothelial growth factor (VEGF) are present." Ex. 1052 at 1.

C. Prior Art

1. **Dixon (Ex. 1007)**

Dixon is an article that was published in a 2009 issue of the peer-reviewed Expert Opinion on Investigation Drugs journal, which is more than one year before the priority date of the '345 patent. Therefore, Dixon qualifies as prior art to the '345 patent.[2]

Dixon also explains that "anti-VEGF therapies for neovascular AMD have largely replaced previous treatment modalities and that "all anti-VEGF agents for neovascular AMD are administered only by intravitreal injection." Ex. 1007 at 2.

Dixon discloses that "[t]he advent of anti-VEGF therapy has significantly improved the safe and effective treatment of neovascular AMD", including ranibizumab and bevacizumab. *Id.* at 1. Though ranibizumab and bevacizumab are effective treatments, "the time and financial burden of monthly injections has led to the initiation of studies to examine the efficacy of alternative dosing schedules." *Id.* Thus, "[t]he development of new drugs for neovascular AMD has … focused on both improving efficacy and extending duration of action." *Id*.

Dixon discloses that for AMD, "[o]ne promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental

[2] Patent Owners have not contested Dixon's status as prior art in related proceedings IPR2021-00881, IPR2022-002298, IPR2022-00258, IPR2022-01225, IPR2023-00532, IPR2023-00442, IPR2022-01226, IPR2023-00533, IPR2023-00566, IPR2023-00739, IPR2024-00201, IPR2023-00884, IPR2024-00260, and IPR2024-00298.

growth factors-1 and -3" and that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." *Id.* at 1, 3. Accordingly, a POSA would have understood that the active ingredient was the same in both the VEGF Trap-Eye and aflibercept presentations and that these presentations are a single or "***one*** promising new drug." *Id.* Dixon further teaches that

> [s]tructurally, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment …. Functionally, VEGF Trap-Eye acts as a receptor decoy with high affinity for all VEGF isoforms, binding more tightly than their native receptors. Unlike anti-VEGF drugs currently in use, VEGF Trap-Eye is designed to inhibit placental growth factors-1 and -2 in addition to all isoforms of VEGF-A.

Id. at 3. Dixon discloses the following "Figure 1"

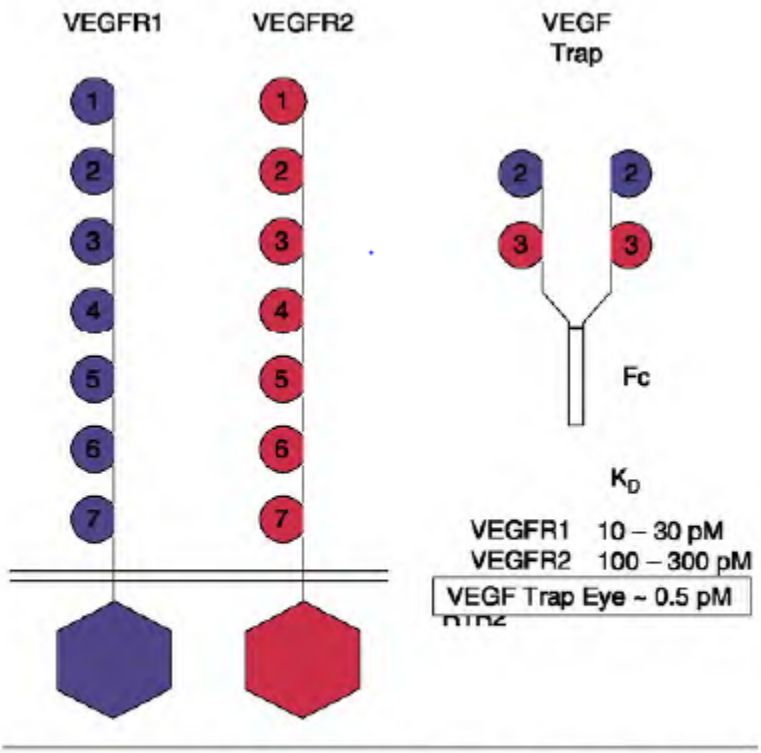

Figure 1. Schematic diagram of VEGF Trap-Eye, a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.

Id. at 4.

Dixon discloses that "low intravitreal dose of 2 mg [VEGF Trap-Eye] allows for extended blocking of VEGF in the eye, but would be predicted to give negligible systemic activity as it will be rapidly bound to VEGF and inactivated." *Id.*

Dixon also discloses the clinical study history for VEGF Trap-Eye. Specifically, Dixon discloses that "[t]he safety, tolerability and biological activity of intravitreal VEGF Trap-Eye in treatment of neovascular AMD was evaluated in the two part [CLEAR-IT-1] study in which "[n]o adverse systemic or ocular events were

noted and visual acuity remained stable or improved ≥ 3 lines in 95% of patients with mean increase in BCVA of 4.6 letters at 6 weeks" while "[p]atients showed substantially decreased foveal thickness." *Id.* "In the second part [of CLEAR-IT-1] patients "received a single intravitreal injection of either 0.5 or 4 mg … and were followed or 8 weeks." *Id.* "No serious adverse events or ocular inflammation was identified during the study. At 8 weeks, the mean decrease in retinal thickness in the low dose group was 63.7 μm compared to 175 μm for the high dose group." *Id.*

Dixon also discloses that "VEGF Trap-Eye has also undergone a small open-label safety study for the treatment of diabetic macular edema (DME)" in which it was "administered as a single 4 mg intravitreal injection to five patients with longstanding diabetes and several previous treatments for DME. The single injection resulted in a median decrease of central macular thickness measured by OCT of 79 μm. BCVA increased by 9 letters at 4 weeks and regressed to a 3 letter improvement at 6 weeks." *Id.*

Citing to NCT-377, Dixon goes on to disclose that VEGF Trap-Eye was the subject of a phase III VIEW 2 trail that "has a similar study design" the VIEW 1 study, which was a "non-inferiority" clinical trial "initiated in August of 2007" in which VEGF Trap-Eye/aflibercept was administered at "2.0 mg at an 8 week dosing interval (following three monthly doses), compared with 0.5 mg of ranibizumab

administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation." *Id.* at 4.

As discussed in the Galanis Report (Ex. 1003 at ¶ 205), Dixon incorporates NCT-377 (Ex. 1018). This is because, Dixon includes a reference to endnote 47:

> evaluation. The VIEW 2 [47] study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America. In both trials, the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).

Ex. 1007 at 4. Endnote 47 is a citation to the clinical trials.gov record for NCT00637377 that was accessed on September 28, 2008:

> 47. VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2). [ClinicalTrials.gov identifier: NCT00637377] ClinicalTrials.gov [online]. Available from: http//clinicaltrials.gov/ct2/show/NCT00637377 [Accessed 28 Sep 2008]

That version of the clinicaltrials.gov record for NCT00637377 is the same as Ex. 1018 that Petitioner relies on for this Petition. Further, the information disclosed in Ex. 1018 as discussed further below provides the specific dosing regimen for the VIEW 2 trial and supports Dixon's discussion of the dosing regimen for that trial as well. Accordingly, Dixon incorporates the information disclosed in Ex. 1018.

2. NCT-377 (Ex. 1018)

NCT-377 is a ClinicalTrials.gov on-line record maintained by the National Library of Medicine at the National Institute of Health ("NIH") disclosing information about the VIEW 2 regimen for aflibercept/VEGF Trap-Eye submitted by Regeneron as of August 4, 2008 and which was current until it was further updated by Regeneron on September 30, 2008. Ex. 1018 at 2.

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." *See,* Ex. 1053 at 2; Ex. 1003 at ¶ 138. NCT-377 is a § 102 printed publication. *Hulu, LLC v. Sound View Innovations,* no. IPR2018-01039, 2019 WL 7000067, *5 (P.T.A.B. Dec. 20, 2019). The Board has found a ClinicalTrials.gov printout analogous to NCT-377 qualifies as a prior art printed publication. *Grunenthal GMBH v. Antecip Bioventures II LLC,* No. PGR2019-00026, 2020 WL 4341822, *8 (P.T.A.B. May 5, 2020). Further, in support of this Petition, Dr. Galanis provides expert opinion that NCT 377 was publicly accessible to a POSA from ClinicalTrials.gov before the priority date of the '345 patent—i.e., August 4, 2008, which is more than one year before January 13, 2011. Therefore, NCT-377 qualifies as prior art to the '345 patent.

NCT-377 provides information for a study titled "Vascular Endothelial Growth (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW2)." Ex. 1017 at 1.

NCT-377 disclosed that the "Assigned Intervention" for "Experimental: Arm 1" of VIEW 2 was "0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks"—meaning aflibercept/VEGF Trap-Eye may be administered every 12 weeks. *Id.* at 8. Similarly, NCT-377 disclosed that the "Assigned Intervention" for "Experimental: Arm 2" of VIEW 2 was "2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks"—meaning aflibercept/VEGF Trap-Eye may be administered every 12 weeks. *Id.* at 7.

NCT-377 also discloses the primary outcome measure of the VIEW 1 trial: "[t]he proportion of subjects who gain at least 15 letters of vision at Week 52." *Id.* at 9.

3. NCT-795 (Ex. 1017)

NCT-795 is a ClinicalTrials.gov on-line record maintained by National Library of Medicine at the National Institute of Health ("NIH") disclosing

information about the VIEW 1 regimen for aflibercept/VEGF Trap-Eye submitted by Regeneron as of April 2009.

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." *See,* Ex. 1053, CT History at 2; Ex. 1003, Galanis Report at ¶¶ 128-29. NCT-795 is a § 102 printed publication. *Hulu,* 2019 WL 7000067, *5. The Board has found a ClinicalTrials.gov printout analogous to NCT-795 qualifies as a prior art printed publication. *Grunenthal*, 2020 WL 4341822, *8. Further, in support of this Petition, Dr. Galanis provides expert opinion that NCT 795 was publicly accessible to a POSA from ClinicalTrials.gov before the priority date of the '345 patent—i.e., April 2009, which is more than one year before January 13, 2011. Therefore, Dixon qualifies as prior art to the '345 patent.

NCT-795 provides information for a study titled "Vascular Endothelial Growth (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 1)." Ex. 1017 at 1.

NCT-795 disclosed that the "Assigned Intervention" for "Experimental: 1" of VIEW 1 was "0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks"—meaning aflibercept/VEGF Trap-Eye may be

administered every 12 weeks. *Id.* at 6. Similarly, NCT-795 disclosed that the "Assigned Intervention" for "Experimental: 2" of VIEW 1 was "2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks"—meaning aflibercept/VEGF Trap-Eye may be administered every 12 weeks. *Id.* at 7.

NCT-795 also discloses the primary outcome measure of the VIEW 1 trial: "[t]he proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline." *Id.* at 9.

4. Regeneron (8-May-2008) (Ex. 1022)

Regeneron (8-May-2008) is a press release published on May 8, 2008, which is more than one year before the priority date of the '345 patent. Therefore, Dixon qualifies as prior art to the '345 patent. Patent Owner has not contested Regeneron's status as prior art in related proceeding IPR2021-00881.

Regeneron (8-May-2008) reported that "Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration." Ex. 1022 at 1. Regeneron (8-May-2008) further reported "In the first year, the VIEW 2 … study will evaluate the safety and efficacy of VEGF Trap-

Eye at doses of 0.5 [mg] and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four. …. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but not more than 4 weeks until the end of the study." *Id*.

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." *Id.*

5. Regeneron (18-Feb-2010) (Ex. 1052)

Regeneron (18-Feb-2010) is February 18, 2010 press release, which is more than one year before the alleged priority date of the '345 patent. Therefore Regeneron (18-Feb-2010) qualifies as prior art to the '345 patent.

Regeneron (18-Feb-2010) discloses "that VEGF Trap-Eye showed positive results in a Phase 2 study in patients with diabetic macular edema (DME). The primary endpoint of the study, a statistically significant improvement in visual acuity over 24 weeks compared to the standard of care in DME, macular laser therapy, was met. Visual acuity improvement was measured by the mean number of letters gained over the initial 24 weeks of the study." Ex. 1022 at 1.

Regeneron (18-Feb-2010) discloses a quote from "Dr. Kemal Malik, member of the Bayer HealthCare Executive Committee" in which he says "The ability of VEGF Trap-Eye to significantly improve vision in patients with DME in this initial Phase 2 study is encouraging," and that "Bayer and Regeneron will discuss the next steps in further developing VEGF Trap-Eye in this indication." *Id.*

Regeneron (18-Feb-2010) also discloses a quote from "Diana Do, MD, the Principal Investigator for the study and Assistant Professor Ophthalmology at the Wilmer Eye Institute, The John Hopkins University School of Medicine in Baltimore, Maryland" in which she states "The magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this Phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema, a disease in which high level of vascular endothelial growth factor (VEGF) are present[.]" *Id.*

6. The '758 patent (Ex. 1012)

The '758 patent issued on May 20, 2008, which is more than one year before the priority date for the '345 patent. Therefore, the '758 patent qualifies as prior art to the '345 patent.

The '758 patent disclosed "[m]odified chimeric polypeptides with improved pharmacokinetic," including, the VEGF $Trap_{R1R2}$ (i.e., VEGF Trap-Eye/aflibercept) fusion protein. Ex. 1012 at Abstract, 19:15-17, 29:39-56. The aflibercept sequence

is disclosed in Figures 24A-C. *Compare* Ex. 1001, SEQ ID NO:1 and SEQ ID NO:2, *with* Ex. 1012, Fig.24A-C; *see also*, Ex. 1049 at 2, 6-7.

The '758 patent also teaches that aflibercept may be useful for treating disorders such as AMD and diabetic retinopathy. Ex. 1012 at 15:61-16:6.

XI. DETAILED ANALYSIS

A. Anticipation

The Challenged Claims are anticipated by each of Dixon and NCT-795. Each reference discloses all limitation of the Challenged Claims.

Anticipation requires 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). "[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers Squibb v. Ben Venue Lab'ys*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). Here, the independent claims require only a dosing regimen without any particular efficacy or result, and therefore, "proof of efficacy is not required in order for a [prior art] reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

For purposes of determining anticipation by a prior-art reference, "[w]hen a reference or material from various documents is incorporated in the prior-art reference, the incorporated items are 'effectively part of the host document as if they were explicitly contained therein'." *Arbutus Bipharma Corp. v. ModernaTC, Inc.,* 65 F.4th 656, 662-63 (Fed. Cir. 2023) *quoting Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) "Incorporation by reference provides a method for integrating material from various documents into a host document—a patent or printed publication in an anticipation determination—by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein." *Advanced Display*, 212 F.3d at 1282. To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky*, 474 F.2d 671, 674 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602–03 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate if one reference "expressly incorporates a particular part" of another reference).

Here, pursuant to endnote 47, Dixon's discussion of the Phase III VIEW 2 trial of VEGF Trap-Eye is based on NCT-377 (Ex. 1018). Ex. 1003 at ¶ 157. In endnote 47, Dixon provides a detailed citation to NCT-377 (Ex. 1018) such that a POSA may identify and may themselves obtain that reference. Therefore, Dixon incorporated by reference NCT-377's disclosures regarding the VIEW 2 trial.

1. Grounds 1-4: Dixon, NCT-377, NCT-795, Regeneron (8-May-2008) Anticipate Claims 1-9 of the '345 Patent

Claims 1-9 are anticipated by each of Dixon, NCT-377, NCT-795, and Regeneron (8-May-2008):

'345 Patent	Prior Art
Claim 1 – A method for treating an angiogenic eye disorder in a patient, said method comprising	**Dixon:** "A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) will enroll ~ 1200 patients with neovascular AMD in the US and Canada" and that the second part "VIEW 2 study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America." Ex. 1007 at 4. **NCT-377:** "A Randomized, Double Masked, Active Controlled, Phase 3 Study of Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects with Neovascular Age-Related

’345 Patent	Prior Art
	Macular Degeneration (AMD).” Ex. 1018 at 5. **NCT-795:** “Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration.” Ex. 1017 at 1, 3, 4. **Regeneron (8-May-2008)**: VIEW 2 trial, a second Phase 3 clinical study in a development program evaluating VEGF Trap-Eye for the treatment of neovascular form of Age related Macular Degeneration (wet AMD), a leading cause of blindness in adults.” Ex. 1022 at 1.
sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	**Dixon:** VIEW 1 and VIEW 2 studies “will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals” and that “[a]fter the first year of the study, patients will enter a second year of p.r.n. dosing evaluation.” Ex. 1007 at 4. In other words, an “initial dose” at day 0; “secondary doses” 4-weeks apart during the first year; and “tertiary doses” administered in second year as p.r.n, which NCT-377 discloses “may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.” Ex. 1018 at 8-9.

’345 Patent	Prior Art
	NCT-377: 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” (Ex. 1018 at 8-9); “2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.” Ex. 1018 at 9. In other words, the “initial dose” at day 0; “Secondary doses” 4-weeks apart during the first year; and “tertiary doses” in the second year that may be administered as infrequently as 12 weeks after the immediately preceding dose. **NCT-795:** “0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks,” (Ex. 1017 at 6); “2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.” *Id.* at 7. In other words, the “initial dose” at day 0; “Secondary doses” 4-weeks apart during the first year; and

’345 Patent	Prior Art
	“tertiary doses” in the second year that may be administered as infrequently as 12 weeks after the immediately preceding dose. **Regeneron (8-May-2008):** “In the first year, the VIEW 2 … study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4 week intervals. After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but no more often than every 4 weeks until the end of the study.” *Id.* at 1. In other words, the “initial dose” at day 0; “Secondary doses” 4-weeks apart during the first year; and “tertiary doses” in the second year that may be administered as infrequently as 12 weeks after the immediately preceding dose.
wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and	**Dixon:** VIEW 1 and VIEW 2 studies “will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals” during the first year. Ex. 1007 at 4 (i.e., the doses at weeks 4, 8, 12, etc. during the first year).

’345 Patent	Prior Art
	NCT-377: “0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year,” (Ex. 1018 at 8-9); “2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year.” *Id.* at 9 (i.e., the doses at weeks 4, 8, 12, etc. during the first year). **NCT-795:** “0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year,” (Ex. 1017 at 6); “2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year.” *Id.* at 7 (i.e., the doses at weeks 4, 8, 12, etc. during the first year). **Regeneron (8-May-2008):** “In the first year, the VIEW 2 … study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4 week intervals. *Id.* at 1 (i.e., the doses at weeks 4, 8, 12, etc. during the first year.
wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;	**Dixon (vis-à-vis NCT-377):** “Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.” Ex. 1018 at 8-9. In other words, tertiary doses—i.e., doses after the first year—may be administered as infrequently as 12 weeks after the immediately preceding dose, including immediately after the last secondary dose of the first year.

’345 Patent	Prior Art
	NCT-795: “Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks.” Ex. 1017 at 6-8. In other words, the tertiary dose—i.e., doses after the first year—may be administered as infrequently as 12 weeks after the immediately preceding dose, including immediately after the last secondary dose of the first year. **Regeneron (8-May-2008):** “After the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, … until the end of the study.” Ex. 1022 at 1. In other words, the tertiary dose—i.e., doses after the first year—may be administered as infrequently as 12 weeks after the immediately preceding dose, including immediately after the last secondary dose of the first year.
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising	A POSA would understand that VEGF Trap Eye (disclosed in Dixon, NCT-377, NCT-795, Regeneron (8-May-2008) is the same as aflibercept and that it is a receptor-based chimeric molecule having the claimed domains. Ex. 1003 at ¶ 157.
an immunoglobin-like (lg) domain 2 of a first VEGF receptor which is Fltl and lg domain 3 of a second VEGF	

’345 Patent	Prior Art
receptor which is Flkl, and a multimerizing component.	**Dixon:** “***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.” *Id.* at 1 (emphasis added). “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure.” *Id.* at 3. VEGF Trap-Eye is “a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.” Ex. 1007 at 4 (Fig. 1).
Claim 2 – The method of claim 1, wherein the VEGF antagonist is aflibercept.	A POSA would understand that VEGF Trap-Eye (disclosed in Dixon, NCT-377, NCT-795, Regeneron (8-May-2008)) is another name for aflibercept. **Dixon:** “***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.” *Id.* at 1 (emphasis added). “VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure.” *Id.* at 3. VEGF Trap-Eye is “a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG.” Ex. 1007 at 4 (Fig. 1).
Claim 3 – The method of claim 1, wherein all doses of the VEGF	A POSA would know that intravitreal administration is a subset of

’345 Patent	Prior Art
antagonist are administered to the patient by intraocular administration.	intraocular administration and refers to administration directly into the vitreous of the eye. Ex. 1003 at ¶ 226.
Claim 4 – The method of claim 3, wherein the intraocular administration is intravitreal administration.	**Dixon**: “[VIEW 1] will evaluate the safety and efficacy of ***intravitreal*** VEGF Trap-Eye at doses of 0.5 and 2.0 mg.” *Id*. at 4 (emphasis added). **NCT-377:** “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.” Ex. 1018 at 5 (emphasis added). **NCT-795:** “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.” Ex. 1017 at 1, 3. **Regeneron (8-May-2008):** “Both View 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by ***intravitreal*** injection.” Ex. 1022 at 1.
Claim 5 – The method of claim 4, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.	**Dixon:** “[VIEW 1] will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg.” Ex. 1007 at 4.

’345 Patent	Prior Art
Claim 6 – The method of claim 5, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.	**NCT-377:** “0.5 mg VEGF Trap-Eye administered every 4 weeks,” (Ex. 1018 at 8); “2.0 mg VEGF Trap-Eye administered every 4 weeks.” *Id.* at 9. **NCT-795:** “0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year,” (Ex. 1017 at 6); “2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year.” *Id.* at 7, 8. **Regeneron (8-May-2008):** “The VIEW 2 … study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of 0.5 milligrams (mg) and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval.” Ex. 1022 at 1.
Claim 7 – The method of claim 5, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.	
Claim 8 – The method of claim 5, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion and corneal neovascularization.	**Dixon:** “A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) will enroll ~ 1200 patients with neovascular AMD in the US and Canada.” Ex. 1007 at 4. **NCT-377: “**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
Claim 9 – The method of claim 8, wherein the angiogenic eye disorder is age related macular degeneration.	

’345 Patent	Prior Art
	Macular Degeneration (AMD).” Ex. 1018 at 5. **NCT-795:** “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.” Ex. 1017 at 1, 3. **Regeneron (8-May-2008):** “In the first year, the VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye.” Ex. 1022 at 1.

Accordingly, Dixon, NCT-377, NCT-795, and Regeneron disclose each of the limitations of claims 1-9 of the ’345 patent, and thus anticipate.

2. Ground 5: Claims 1-9 are obvious over Dixon in view of NCT-377

To the extent the PTAB determines Dixon does not incorporate the information disclosed in NCT-377, claims 1-9 are obvious over Dixon in view of NCT-377. As already noted above, Dixon specifically cites and refers to NCT-377 and each discloses information about the VIEW 2 phase III clinical study. Therefore a POSA would have been motivated to combine the teaching discloses therein with a reasonable expectation of success. Further as shown above in Section C.1, Dixon

and NCT-377 together disclose each of the limitations recited in claims 1-9 of the '345 patent.

Accordingly, claims 1-9 are obvious over Dixon in view of NCT-377.

3. Grounds 6-9: Claims 10 and 11 are obvious over any one of Dixon, NCT-377, NCT-795, or Regeneron (18-May-2008) in view of Regeneron (8-May-2010) and a POSA's knowledge.

Claims 10 and 11 depend from claims 8, 5, 4, and 1. As discussed above, each of Dixon, NCT-377, NCT-795, and Regeneron (18-May-2008) discloses each and every element of Claims 1-9. Therefore, the only limitation from claims 10 and 11 that are not explicitly disclosed in these prior art references is the application of the claimed method recited in claim 8 for the treatment of diabetic retinopathy and DME. A POSA, however, would have been motivated with a reasonable expectation of success to apply the method of claim 8 disclosed in Dixon, NCT-377, NCT-795, and Regeneron (18-May-2008) to the treatment of DME (which necessarily includes diabetic retinopathy) in view of Regeneron (8-Feb-2010), and a POSA's knowledge.

No specific efficacy is required by any of the Challenged Claims, and more than one year before the alleged November 2011 priority date of the '345 patent, Regeneron published a press release reporting "VEGF Trap-Eye Shows Positive Results in a Phase 2 Study in Patients With Diabetic Macular Edema." Ex. 1052 at

1. It further summarized the mean gain in visual acuity at week 24 dosing arm and the mean number of treatments received by patients over the first six monthly visits:

- VEGF Trap Eye 0.5 mg monthly (n=44; 5.6 injections): +8.6 letters gained
- VEGF Trap-Eye 2 mg monthly (n=44; 5.5 injections): +11.4 letters gained
- VEGF Trap-Eye 2 mg every other month, following 3 monthly injections (n=42: 3.8 injections): +8.5 letters gained
- VEGF Trap-Eye 2 mg as-needed, following 3 monthly injections (n=45; 4.4 injections): +10.3 letters gained

Id. This data, including especially the data for patients receiving "VEGF Trap-Eye 2 mg as needed" would have been enough to motivate a POSA to apply the dosing regimen disclosed in each of Dixon, NCT-277, NCT-795, and Regeneron (8-May-2008) to the treatment of DME with a reasonable expectation of success. In fact, POSAs reviewing that data asserted that "[t]he ability of VEGF Trap-Eye to significantly improve vision in patients with DME in this initial Phase 2 study is encouraging" and "[t]he magnitude of the gain in visual acuity achieved with VEGF Trap-Eye in this Phase 2 study demonstrates the biologic activity of VEGF Trap-Eye in treating diabetic macular edema." *Id*.

Moreover, a POSA would have been motivated to apply the dosing regimen disclosed by Regeneron for the treatment of diabetic retinopathy, including diabetic

macular edema (DME) because (i) AMD and diabetic retinopathy share the same pathogenesis; (ii) VEGF Trap-Eye/aflibercept targets the shared pathogenesis; (iii) there was a desire to reduce the frequency of intravitreal injections in the treatment of diabetic retinopathy; and (iv) VEGF Trap-Eye/aflibercept had been shown to be effective in treated diabetic retinopathy from less frequent administrations. Ex. 1003 at ¶¶ 240-41.

The prior art demonstrates that POSAs knew that AMD and diabetic retinopathy share the same pathogenesis—in particular that expression of vascular endothelial growth factor or "VEGF" results in angiogenesis in the eye leading to AMD and diabetic retinopathy. Ex. 1001 at 1:31-54; Ex. 1007 at 2; Ex. 1043 at [0003], [0074]; Ex. 1032 at 4; Ex. 1024 at 2; Ex. 1026, at 1-2. The prior art also widely recognized that VEGF Trap-Eye/aflibercept is a VEGF-antagonist that targets VEGF to limit angiogenesis. Ex. 1001 at 1:57-60; Ex. 1007 at 1-2; Ex. 1012 at 3:8-13; Ex. 1026 at 1.

The prior art also demonstrates that VEGF-antagonists other than VEGF Trap-Eye/aflibercept were being used for the treatment of angiogenic eye disorders such as AMD and diabetic retinopathy in particular, but that these drugs required frequent administration. Ex. 1007 at 2; Ex. 1012 at 15:50-16:6; Ex. 1043 at Claim 21; Ex. 1044 at 5. Thus, as of the alleged priority dates, POSAs were looking to identify

and develop VEGF antagonists that required less frequent administration. Ex. 1006, at 7; Ex. 1007 at 2, 5; Ex. 1045 at 16-18.

The prior art further demonstrates the drawbacks to frequent intravitreal injections, including risk of injection-related complications, pain, and financial burden—recognized concerns with traditional dosing regimens for angiogenic eye disorders (Ex. 1007 at 2, 15; Ex. 1045 at 16-18), motivating the skilled artisan to pursue less frequent dosing schedules compared to the monthly dosing often used for other anti-VEGF therapeutics.

As of the alleged priority dates, POSAs also recognized VEGF Trap-Eye/aflibercept as "represent[ing] the most promising anti-VEGF" and that it "may have longer duration of effect in the eye." Ex. 1007 at 5. Published data showed that VEGF Trap-Eye/aflibercept was effective in the treatment of diabetic retinopathy at a dose of 2.0 or 0.5 mg. *Id.* at 4. Regeneron also publicized that it was conducting further studies with VEGF Trap-Eye for the treatment of diabetic retinopathy, including DME. Ex. 1037 at 19; Ex. 1039 at 2; Ex. 1040 at 1.

Therefore, based on the prior art and a POSA's knowledge, there was a motivation with a reasonable expectation of success to administer VEGF Trap-Eye/aflibercept for the treatment of diabetic retinopathy including DME according

to the prior art dosing and administration regimen used in the VIEW 1 and VIEW 2 studies disclosed by Regeneron.

Accordingly, any one of Dixon, NCT-277, NCT-795, and Regeneron (8-May-2008) in view of Regeneron (18-Feb-2008) and a POSA's knowledge render obvious claims 9 and 10 of the '345 patent.

* * *

Each anticipatory and obviousness reference asserted herein is presumed enabling and it is Patent Owner'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) (rejecting patentee non-enablement arguments where reference disclosed exact dosing amount and interval in claims, thus inherently disclosing the claimed "minimizing skeletal muscle toxicity"). Rebuttal here would be futile because each reference clearly sets forth a dosing regimen that a POSA would have no trouble following. Moreover, the Challenged Claims' preamble does not help Patent Owner; nor would Regeneron's potential proposed construction of "tertiary dose," should Patent Owner attempt to propose the construction in this IPR that it proposed in IPR2021-00881. The VEGF Trap-Eye/aflibercept Phase 2 data show "treating" of AMD with VEGF Trap-Eye.

Further, any attempt by Patent Owner to argue that any of the references discussed herein do not render the Challenged Claims anticipated or obvious because they describe "experimental uses" must fail. Patent Owner made this very same argument during the proceedings for IPR2021-00881. In that case, the PTAB determined:

> Based on our consideration of the record as a whole, we do not find Patent Owner's argument that Dixon is subject to the experimental use exception persuasive …. We emphasize here that Dixon is a printed publication that discloses each element of the claimed invention. In particular, the reference discloses treating an angiogenic eye disorder by administering VEGF-Trap Eye according to the dosing regimen recited by the challenged claims to the patient. Dixon concludes that "[a]nti-VEGF therapy has vastly improved the treatment of neovascular AMD in terms of both safety and efficacy." …. Based on those disclosures, Patent Owner's position that Dixon did not place the claimed invention into the public domain because Dixon did not disclose "whether the claimed method works for its intended purpose" fails. As discussed above, we have found that the intended purpose of the claimed methods is to treat an angiogenic eye disorder and that such treatment only requires administering the recited dosing regimen to a patient for that purpose, without any requirement that such treatment achieves any particular level of efficacy. Thus, Patent Owner has not established that Dixon is unavailable as anticipatory prior art because Dixon did not disclose an unclaimed feature for the method of treating, i.e., a particular level of effectiveness.

Ex. 1015 at 44-45. *See also,* Ex. 1014 at 86 ("with respect to Patent Owner's argument that Dixon does not anticipate the challenged claims because it describes

an experimental use, we considered this argument in the -0881 Decision and rejected it. …. The intended purpose of the claimed methods is to treat an angiogenic eye disorder and that such treatment only requires administering the recited dosing to a patient for that purpose, without any requirement that such treatment achieves any particular level of efficacy."). Therefore, for the same reasons explained by the PTAB, any such defense in this case must also be rejected.

Any attempt by Patent Owner to argue that Dixon, NCT-377, NCT-795, Regeneron (8-May-2008) and/or Regeneron (18-Feb-2010) cannot anticipate or render obvious the Challenged Claims because they lack utility must also fail. Patent Owner made this very same argument during the proceedings for IPR2021-00881. In that case, the PTAB determined:

> Based on our consideration of the record as a whole, Patent Owner's argument that Dixon cannot be anticipatory because it lacks utility is not well-taken as it is insufficiently supported. Dixon describes the use of VEGF Trap-Eye in a method for treating an angiogenic eye disorder in a patient. … For such therapy, Dixon reports "Phase I and II trial data indicating safety, tolerability and efficacy." …. Whether those results "correspond to a dosing regimen encompassed by the Challenged Claims," is immaterial, as we have determined that the challenged claims do not recite or otherwise require any particular level of efficacy. Moreover, as the Federal Circuit has explained, "a prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005). "As long as the

> reference discloses all of the claim limitations and enables the 'subject matter that falls within the scope of the claims as issue,' the reference anticipates—no 'actual creation or reduction to practice' is required." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quoting *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1380–81 (Fed. Cir. 2003)).

Ex. 1015 at 43-44. Therefore, for the same reasons explained by the PTAB, any such defense in this case must also be rejected.

XII. DISCRETION UNDER § 325(D) AND § 314

Consistent with the guidance provided by "FAQs for Interim Processes for PTAB Workload Management," Petitioner does not present affirmative arguments in anticipation of what Patent Owner may argue by way of briefing seeking discretionary denial. Petitioner will present arguments in an Opposition Brief, should Patent Owner elect to file a Discretionary Denial Brief.

XIII. SECONDARY CONSIDERATIONS DO NOT OVERCOME STRONG EVIDENCE OF OBVIOUSNESS

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 present herein, and they cannot overcome the strong prima facie case of obviousness discussed above. *See Wyser v. Master Lock Co.,* 616 F.3d 1231, 1246 (Fed. Cir. 2010).

As an initial matter, there is no nexus between any supposed secondary considerations and any aflibercept product, including Elyea® and Eylea HD®—Regeneron's aflibercept products that are currently on the market. Claims 10 and 11 of the '345 patent require the administration of about 0.5 mg to about 2 mg of a VEGF antagonist for the treatment of diabetic retinopathy (claim 10) or DME (claim 11), wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.

With respect to DME and DR, the prescribing information for Eylea® does not suggest healthcare professionals to administer the drug 12 weeks apart. Instead, it suggests administration "every 4 weeks … for the first 5 injections followed by 2 mg … once every 8 weeks":

- **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)**
  - The recommended dose for EYLEA is 2 mg (0.05 mL of 40 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL of 40 mg/mL solution) via intravitreal injection once every 8 weeks (2 months). (2.7, 2.8)

Ex.1054 at Dosage and Administration.

As for Eylea HD®, the prescribing information for that product, does not suggests administering a dose of between about 0.5 mg to about 2 mg of the VEGF antagonist for the treatment of DR or DME. Instead, it recommends a dose of 8 mg, which is not within the claimed about .5 to about 2 mg dose:

- **Diabetic Macular Edema (DME)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.3)
- **Diabetic Retinopathy (DR)**
  - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 12 weeks, +/- 1 week. (2.4)

Ex. 1055 at Dosage and Administration.

Additionally, both Eylea® and Eylea HD® are also indicated for the treatment of angiogenic eye disorders other than DME and DR—i.e., AMD—which has its own recommended dosage and administration suggestions. Therefore, patent owner would be required to distinguish between which indication and suggested dosage and administration contributes to any supposed secondary considerations.

Moreover, claims 10 and 11 do not require any particular levels of efficacy, and therefore there cannot be any unexpected results. And in any event, as discussed above, there was a reasonable expectation that administration of aflibercept according to the dosing regimens recited in claims 10 and 11 would result in the treatment of DR and DME. Ex.1003 at ¶¶ 311-312.

XIV. CONCLUSION

For the foregoing reasons, Petitioner has established a reasonable likelihood that claims 1-1 are unpatentable. Petitioner therefore respectfully requests that *inter partes* review of the ’345 patent be granted.

Dated: July 14, 2025

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,828,345 complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) and (b)(1)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, it contains 12,078 words as counted by the word processing program used to prepare the paper.

Date: July 14, 2025

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on July 14, 2025, a complete and entire copy of this Petition for *Inter Partes* Review of U.S. Patent No. 10,828,345, Power of Attorney, and all supporting exhibits were provided via Federal Express to the Patent Owner at the correspondence address of record as follows:

By electronic mail to: dberl@wc.com

By Federal Express Next Business Day Delivery to :
191459 - A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743

/s/ Nicole S. Lynch
Nicole S. Lynch