UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOCON BIOLOGICS, INC. and
BIOCON BIOLOGICS LIMITED,
Petitioners

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

U.S. Patent No. 12,168,036 to Graham

Issue Date: December 12, 2024

Title: Methods for Treating Angiogenic Eye Disorders with High Doses of VEGF Receptor Fusion Proteins

Post Grant Review No. PGR2026-00039

PETITION FOR POST GRANT REVIEW OF U.S. Patent No. 12,168,036

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1004	Declaration of Dr. Robert J. Falconer
1005	U.S. Patent No. 7,608,261 (Furfine)
1006	U.S. Patent No. 8,921,316 (Dix)
1007	U.S. Publication No. 2016/0144025 A1 (Vitti)
1008	Center for Drug Evaluation and Research, "Clinical Pharmacology and Biopharmaceutics Review(s)" App. No. 125387Orig1s000 (2011) ("2011 Eylea® Clinical Review")
1009	Product Information EYLEA® aflibercept (rch), ("AU Eylea® Label")
1010	U.S. Publication No. 2015/0071920 A1 (Larson)
1011	U.S. Publication No. 2017/0232199 A1 (Fiedler)
1012	WO 2016/154288 (Ingber)
1013	PTE Application U.S. Patent No. 7,374,758, (App. No. 11/016,503)
1014	Robert L. Avery, MD et al., *INTRAVITREAL INJECTION TECHNIQUE AND MONITORING Updated Guidelines of an Expert Panel,* Retina, J. Retinal and Vitreous Diseases, 34, S1-S18 (2014).
1015	Sahar Awwad et al., *Principles of Pharmacology in the Eye,* 174 Brit. J. Pharmacol. 4205 (2017).
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1017	CATT Research Group, *Ranibizumab and bevacizumab for Neovascular Age-Related Macular Degeneration,* 364 NEJM 1897 (2011).
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1020	Arup Das, Paul G. McGuire & Sampathkumar Rangasamy, *Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets*, Ophthalmology (2015).
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1024	K Ghasemi Falavarjani & QD Nguyen, *Adverse Events and Complications Associated with Intravitreal Injection of Anti-VEGF Agents: a Review of Literature*, Eye (2013).
1025	Feng He et al., *Effect of Sugar Molecules on the Viscosity of High Concentration Monoclonal Antibody Solutions*, 28 Pharm. Res. 1552 (2011).
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1029	Su-Eon Jin & Sung-Joo Hwang, *Ocular Delivery Systems for the Administration of Antibody Therapeutics*, J. Pharm. 47 Investig. 373 (2017).
1030	Lehman Brothers Presentation, 9th Annual Global Healthcare Conference, Mar. 2006

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1031	Joan W. Miller, Saghar Bagheri & Demetrios GF Vavvas, *Advances in Age-related Macular Degeneration Understanding and Therapy,* 10 U.S. Ophthalmic Rev. 119 (2017).
1032	Chakravarthy Narasimhan, Henryk Mach & Mohammed Shameem, *High-Dose Monoclonal Antibodies Via the Subcutaneous Route: Challenges and Technical Solutions, an Industry Perspective,* 3 Therapeutic Delivery 889 (2012).
1033	Martin S. Neergaard et al., *Viscosity of High Concentration Protein Formulations of Monoclonal Antibodies of the IgG1 and IgG4 Subclass – Prediction of Viscosity Through Protein-Protein Interaction Measurements,* 49 European J. Pharm. Sci. 400 (2013).
1034	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).
1035	Quan Dong Nguyen, et al., *Evaluation of Very High- and Very Low-Dose Intravitreal Aflibercept in Patients with Neovascular Age-Related Macular Degeneration*, 28 J. Ocular Pharmacology and Therapeutics 581 (2012).
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1037	Lorena Perez-Gutierrez & Napoleone Ferrara, *Biology and therapeutic targeting of vascular endothelial growth factor A*, Nature Reviews Molecular Cell Biology (2023).
1038	Branden A. Salinas et al., *Understanding and Modulating Opalescence and Viscosity in a Monoclonal Antibody Formulation*, 99 J. Pharm. Sci. 82 (2010).
1039	Michael W. Stewart, *Clinical and Differential Utility of VEGF Inhibitors in Wet Age-Related Macular Degeneration: Focus on Aflibercept,* 6 Clin. Ophthalmol. 1175 (2012).
1040	Lisa L. Sun, Todd Goodwin, and Joseph J. Park, *Optical coherence tomography changes in macular CMV retinitis,* 18 Dig. J. Ophthalmol. 1 (2012).
1041	George Trichonas & Peter K. Kaiser, *Aflibercept for the Treatment of Age-Related Macular Degeneration*, 2 Ophthalmol. Ther. 88 (2013).
1042	Rohit Varma, et al., *Prevalence of and Risk Factors for Diabetic Macular Edema in the United States*, 132 JAMA Ophthalmol. 1334 (2014).

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1043	Dabir S. Viswanath et al., *Correlations and Estimation of Pure Liquid Viscosity*, Viscosity of Liquids: Theory, Estimation, Experiment, and Data (2007).
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1045	Shawn Shouye Wang, Yifei (Susie) Yan, and Kin Ho, *US FDA-Approved Therapeutic Antibodies with High-Concentration Formulation: Summaries and Perspectives*, 4 Antibody Therapeutics 262 (2021).
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1062	Napoleone Ferrara, *Vascular endothelial growth factor and age-related macular degeneration: from basic science to therapy*, Nature Medicine (2010).
1063	Roomasa Channa, Michael Smith & Peter A Campochiaro, *Treatment of macular edema due to retinal vein occlusions*, Clinical Ophthalmology (2011).
1064	William Rhoades et al., *Management of macular edema due to central retinal vein occlusion – The role of aflibercept*, Taiwan J. Ophthalmol (2017).
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1070	*Alvotech USA Inc. et al v. Regeneron Pharms., Inc.*, PTAB-PGR2025-00085 Order No. 10.

Biocon Biologics, Inc. and Biocon Biologics Limited., ("Petitioner") petitions for Post-Grant Review ("PGR") of claims 1-38 ("challenged claims") of U.S. Patent No. 12,168,036 ("the '036 patent," EX1001) assigned to Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron"). In particular, Petitioner respectfully seeks to join the instituted Alvotech PGR (PGR2025-00085) as a party pursuant to the joinder provisions of §42.222(b), as explained in the motion for joinder filed with this Petition.

This Petition is substantively identical to Alvotech's petition filed in PGR2025-00085 (EX1069), except for Petitioner-specific mandatory notices and minor changes to comply with word limitations.

I. INTRODUCTION

Because eye injections carry great risks, including potential blindness, persons of skill in the art ("POSA") have long known to minimize frequency of such injections. This PGR concerns Regeneron's obvious solution to minimizing injection frequency for its multi-billion dollar franchise EYLEA®: namely, raising the concentration of the drug, aflibercept, over its prior art product. The challenged patent claims little more than that and is plainly obvious over extensive prior art.

Regeneron first marketed EYLEA over a decade ago, and its drug is covered by many patents—dating back to 2005. EX1003, ¶59. The Board is no stranger to

those patents; many have been successfully challenged.[1] While Regeneron chose a low concentration and dose for EYLEA, its early disclosures were not so limited—they also taught, and claimed, higher concentrations and doses. This is no surprise, as high-concentration formulations had meaningful benefits, including reducing injection frequency. This was desirable because intravitreal injections, along with being uncomfortable and inconvenient, carry a small but significant risk of serious side effects due to injection site reactions. EX1003, ¶¶70-76. High-concentration formulations of aflibercept (100 mg/ml or more) would allow for higher doses to be administered in one injection, so the drug would last longer and reduce the frequency of injections.

With its early patents nearing expiration, Regeneron launched, in 2023, a "high-concentration" or "high-dose" EYLEA "HD." EYLEA HD contains a higher concentration of aflibercept—114.3 mg/ml—in a volume of 70 microliters for an 8mg administered dose.

Even though Regeneron had repeatedly disclosed high-concentration formulations of aflibercept, including 100 mg/ml and higher, along with the high doses, including up to 10 mg, Regeneron chose to file a new application, in 2021,

[1] In twelve different challenges involving nine patents, claims were found unpatentable or were disclaimed by Regeneron.

purporting to cover its "high-concentration" and "high dose" EYLEA product. And, despite its prior disclosures, Regeneron successfully obtained the '036 patent by convincing the Examiner that it had optimized known formulation parameters to make its high concentration, high dose formulation workable. Specifically, Regeneron convinced the Examiner that it had discovered that the higher-concentration formulations had problems with viscosity, and that Regeneron solved that problem. Neither are correct.

On the one hand, there was no viscosity problem to be solved for high-concentration aflibercept formulations—only a known suitable viscosity range. The claimed target viscosity was nothing new, but instead was known in the art and disclosed in the Larson prior art reference, which was never before the Examiner. And Regeneron stated that its prior art, high concentration formulations were suitable for eye injection (i.e., had a suitable viscosity).

On the other hand, Regeneron doesn't claim a viscosity-problem solution. The '036 patent specification states that the presence of known viscosity reducing agents (e.g., arginine) has no impact on viscosity. In fact, the only formulation component mentioned by the specification as impacting viscosity is a buffer. And only in the context that a histidine buffer achieves a lower viscosity than a phosphate buffer. But the '036 patent claims are ***entirely silent*** as to any viscosity-problem solving formulation component: the claims are not limited to any preferred buffer, cover all

buffers, and, in fact, encompass formulations with no buffer.

For the reasons set forth below, the Board should find all claims unpatentable.

II. BACKGROUND

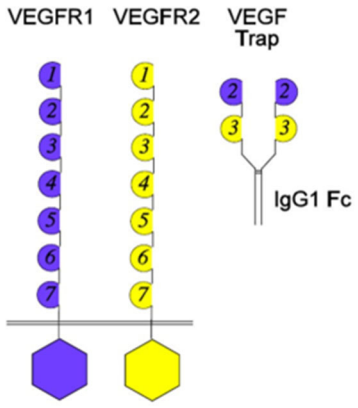
The '036 patent concerns pharmaceutical formulations of VEGF receptor fusion protein antagonists ("VEGF antagonists" or "anti-VEGF") used to treat serious eye disorders resulting from excessive blood vessel growth ("angiogenic eye disorders"). The '036 patent is just one of over 50 Regeneron patents that claim anti-VEGF, methods of making anti-VEGF, methods of treating eye disorders with anti-VEGF, and dosing regimens. These patents all relate to Regeneron's EYLEA (aflibercept) product.

Aflibercept is a VEGF antagonist, a type of biologic that works in the eye by neutralizing vascular endothelial growth factor ("VEGF")—a protein that stimulates the growth of new blood vessels (angiogenesis). EX1003, ¶¶23-25, 41-42. Other well-known VEGF antagonists include ranibizumab (Lucentis®) and bevacizumab (Avastin®). EX1003, ¶¶67-68.

VEGF is essential for normal development of eye vasculature. EX1003,¶25. But excess VEGF can cause abnormal and leaky blood vessels to form in the retina. EX1003, ¶25. These abnormal vessels can leak fluid and blood and eventually lead to serious angiogenic eye disorders like age-related macular degeneration (AMD) and diabetic macular edema (DME). EX1003, ¶¶25-38.

To treat these conditions, doctors inject VEGF antagonists like aflibercept directly into the eye ("intravitreal injection"). EX1003, ¶70. Aflibercept binds to VEGF preventing VEGF from attaching to VEGF receptors on blood vessel cells and stimulating angiogenesis in the eye. EX1003, ¶¶23-25, 41. Once absorbed into circulation, aflibercept presents as "free" (unbound to VEGF) and, more predominantly, as stable inactive aflibercept: VEGF complex. EX1003, ¶42. Because the eye continues to produce VEGF, repeated injections of VEGF antagonist are necessary to maintain therapeutic effects over time. EX1003, ¶77.

Aflibercept is a fusion protein created from the fusion of immunoglobulin-like (Ig) domain 2 of the human VEGF receptor R1 ("VEGFR1") and Ig domain 3 of the human VEGF receptor R2 ("VEGFR2") with the Fc portion of human IgG antibody, as shown below:



EX1009, 1.

In addition to "VEGF Trap," aflibercept was known in the art as "VEGF Trap R1R2" and "VEGFR1R2-FcΔC1(a)." EX1007, ¶86; EX1013, 2. D'Amico explains

a POSA would have known that VEGF $Trap_{R1R2}$, VEGFR1R2-FcΔC1(a), and VEGF Trap are different names for the same fusion protein—aflibercept. EX1003, ¶¶325-326. This is the same fusion protein recited in the '036 patent. EX1003, ¶¶96, 199-203, 219-220, 299-304, 323-326.

III. SUMMARY OF THE '036 PATENT

A. The '036 Patent

The '036 patent, titled "Methods for Treating Angiogenic Eye Disorders With High Doses of VEGF Receptor Fusion Proteins," issued on December 17, 2024. EX1001, codes [45], [54]; EX1003, ¶¶92-100. The '036 patent relates to pharmaceutical formulations containing high concentrations of VEGF receptor fusion protein, such as aflibercept, for treating angiogenic eye disorders. *Id.*, 4:4-5; 8:22-23.

The '036 patent's formulations generally include five ingredients: a VEGF receptor fusion protein, a buffer, a thermal stabilizer, a viscosity reducing agent, and a surfactant. *Id.*, 2:34-36. But the '036 patent also discloses "other embodiments" in which the thermal stabilizer and/or viscosity reducing agent can be "excluded" (although exclusion of a buffer is never mentioned). *Id.*, 2:35-38, 2:47-29. The specification also teaches the formulations should have a pH and a viscosity (from about 5 to 15 cP at 20ºC) suitable for intravitreal injection. *Id.*, 2:38-39.

The '036 patent provides 89 formulations labeled "Formulation A" through

"Formulation KKKK." *Id.*, 23:22-28:25. In addition to the VEGF receptor fusion protein, each of these formulations includes at least a buffer. *Id.* The '036 patent defines buffers as "solutions that resist pH change," and names histidine-based, phosphate-based, acetate-based, and citrate-based buffers as examples. *Id.*, 18:49-50, 18:58-19:1. Every example in the '036 patent includes a buffer.

The '036 patent states that formulations having higher protein concentration were desirable over lower-concentration formulations because they "allow for shorter injection times, smaller injection volumes, lower frequency of antibody administration, and more efficient manufacturing and storage utility." *Id.*, 1:55-58. But the '036 patent acknowledges that higher-concentration formulations, generally, run the risk of increased protein aggregation, higher-viscosity, and decreased stability. *Id.*, 1:58-65.

The '036 patent states that there was "little variation … with the presence of a viscosity reducing agent at all" (*id.,* 38:43-47) and that the ***buffer histidine*** "led to a beneficial decrease in viscosity" relative to a ***phosphate-based buffer*** (*id.*, 13:31-33). Yet even though buffers like histidine had a significant impact on viscosity (even where viscosity reducing agents did not), the claims do not require a buffer, or any other excipient.

B. Prosecution History

The '036 patent was filed on July 23, 2021, as Application No. 17/384,070.

See EX1001, codes [21], [22]. The earliest priority application was filed on May 10, 2018. *Id.*, [60].

In the only Office Action, the Examiner rejected the claims under §112(a) for lack of written description, among other grounds. EX1002, 2140-2148. The Examiner stated the claims "recite[] a high concentration of a VEGF receptor fusion protein without any recitation of the elements of the composition that permit such a high concentration of the protein." *Id.*, 2145. The Examiner stated that "while the specification provides adequate written description for stable, high concentration formulations of a VEGF receptor fusion protein along with 5% sucrose, polysorbate, a histidine-based buffer, and L-arginine, it does not provide adequate written description for the breadth of the formulation encompassed by the claims." *Id.*

In response, Regeneron amended the claims to recite three additional limitations: a ***volume*** of "about 100 microliters or less," a ***protein concentration*** of "at least 100 mg/ml of the VEGF receptor fusion protein," and a ***viscosity*** of "about 5-15 centiPoise (cP) at 20ºC." *Id.*, 758. Regeneron argued that it optimized each of these three "interrelated factors" to produce a formulation suitable for intravitreal injection. *Id.*, 764.

Regeneron argued: (a) the size of the eye's vitreous chamber constrained the injection volume to "about 100 microliters of less," (b) a smaller volume necessarily required a higher concentration of protein, (c) higher protein concentration leads to

higher formulation viscosity; and (d) because the formulation must be pushed through a syringe containing a narrow bore needle for injection into the eye, the higher viscosity caused "damaging shearing forces to the protein" and "difficulty for the clinician who delivers the injection." *Id.* Regeneron argued that, despite "being constrained by these factors," it successfully developed several formulations "including a variety of excipients" (without explaining or claiming what those excipients are) having an acceptable viscosity between 5 and 15 cP. *Id.*, 764-765.

Thereafter, the Examiner allowed the claims. *Id.*, 692-698; EX1003, ¶102-109.

IV. REQUIREMENTS FOR PGR

A. Grounds for Standing

Pursuant to 37 C.F.R. §42.204(a), Biocon certifies that, while the '036 patent issued more than 9-months ago and would not ordinarily be available for a PGR, under the present circumstances—because the Alvotech instituted a PGR on the '036 patent on March 3, 2026—the '036 patent is available for PGR under 37 C.F.R. §42.222(b), which permits requests for joinder "no later than one month after the institution date of any post-grant review for which joinder is requested," here April 3, 2026. Thus, Biocon respectfully requests that it be joined to Alvotech's PGR as a party by virtue of the joinder provisions of 37 C.F.R. §42.222(b). Biocon believes this issue to be one of first impression—i.e., whether 37 C.F.R. §42.222(b) permits a party to

join a PGR proceeding that is not within the 9-month window for filing a PGR.

Biocon is not barred or estopped from requesting PGR challenging claims 1-38.

B. Identification of Challenge

Pursuant to 37 C.F.R. §42.204(b), Petitioner requests PGR and cancellation of the Challenged Claims on the following grounds:

Ground	Claims	35 U.S.C. §	Reference(s)/Basis
1	1, 4-38	103	Vitti, AU EYLEA Label, Larson
2	1, 4-38	103	Furfine, Dix, AU EYLEA Label, Fiedler, Larson
3	1-38	112(a)	Lack of Written Description
4	2, 3	103	Vitti, AU EYLEA Label, Larson, 2011 EYLEA Clinical Review
5	2, 3	103	Furfine, Dix, AU EYLEA Label, Fiedler, Larson, 2011, EYLEA Clinical Review

Declarations from Donald D'Amico, M.D. (EX1003) and Robert Falconer, Ph.D. (EX1004) support the Grounds set forth here. Solely to preserve its right to rely on expert testimony if Alvotech settles, Petitioner relies on accompanying Declarations by Jay Stewart, M.D. (EX 1067), adopting the opinions of Dr. D'Amico, and Barrett Rabinow, Ph.D. (EX 1068), adopting the opinions of Dr. Falconer.

V. PERSON OF ORDINARY SKILL

A POSA at the time of the invention would have been a multidisciplinary team that included (1) a medical doctor in ophthalmology or a similar field with knowledge of angiogenic eye disorders, including treatments and dosing regimens of drugs for intravitreal injection including-anti-VEGF drugs, at least several years conducting research on anti-VEGF treatments for angiogenic eye disorders, and familiarity with the pharmacological properties of anti-VEGF treatments; and (2) a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture, and characterization of therapeutic proteins, including for example, fusion proteins or antibodies. EX1003, ¶¶89-91. The POSA would have also had access to other individuals typically employed in developing protein active pharmaceutical ingredients and products, including those involved in upstream and downstream manufacturing, analytical chemistry, pharmacokinetics, clinical testing, pharmaceutical packaging, and regulatory affairs. EX1003, ¶90.

VI. CLAIM CONSTRUCTION

For purposes of this PGR, no claim terms need construction. EX1003, ¶¶112-114.

VII. KEY PRIOR ART

The following prior-art references show that all claim limitations are found in

the prior art per 37 C.F.R. §42.204(b)(4).

A. Furfine (EX1005)

Furfine, a Regeneron patent titled "VEGF Antagonist Formulations Suitable for Intravitreal Administration," issued on October 27, 2009, as U.S. Patent 7,608,261 B2. EX1005, codes [10], [45], [54]; EX1003, ¶145; EX1004, ¶97. Furfine is prior art under 35 U.S.C. §§102(a)(1) and (a)(2).

Furfine discloses the same anti-VEGF claimed in the '036 patent—i.e., "VEGF trap" or aflibercept. EX1001, 15:51-67; EX1005, 1:32-37, 1:58-2:3; EX1003 ¶146; EX1004, ¶99. In multiple embodiments, Furfine teaches a "stable liquid ophthalmic formulation" comprising 1-100 mg/ml VEGF antagonist. EX1005, 2:4-9; EX1003, ¶147. Furfine additionally claims an ophthalmic formulation comprising "1-100 mg/ml of a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4." EX1005, 19:31-34, EX1002; EX1004, ¶99; EX1003, ¶147. Furfine specifically lists one example with a VEGF antagonist concentration of about 80 mg/ml. EX1005, 2:55-60, 3:29-36; EX1003, ¶147

Furfine "is directed to pharmaceutical formulations suitable for intravitreal administration" (*id.*, 1:15-17) and teaches its formulations may be "provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration." *Id.*, 4:65-67; EX1004, ¶100; EX1003, ¶148. Furfine teaches "the invention provides a stable pharmaceutically acceptable formulation" suitable for ophthalmic use and

reports stability data for certain formulations. EX1005, 6:28-32, 7:35-12:25; EX1004, ¶¶98-99.

B. Dix (EX1006)

Dix, a Regeneron patent titled "Stable Liquid VEGF Antagonist Formulations," issued on December 30, 2014, as U.S. Patent 8,921,316 B2. EX1006, codes [10], [45], [54]; EX1003, ¶149. Dix is prior art under 35 U.S.C. §§102(a)(1) and (a)(2).

Dix discloses the same anti-VEGF recited in the claims of the '036 patent—i.e., "VEGF trap" or aflibercept. EX1001, 15:51-67; EX1006, 1:35-40, 1:56-65; EX1003, ¶150; EX1004, ¶101; EX1003, ¶150. Dix teaches that an aspect of the invention is a "high concentration stable liquid formulation of a VEGF antagonist." EX1006, 2:20-21; EX1004, ¶103; EX1003, ¶¶151-153.

Dix teaches lyophilized formulations of VEGF antagonist that may be reconstituted into liquid solutions. EX1006, 5:54-6:39. In Example 4, a lyophilized formulation was reconstituted into a liquid formulation having a concentration of 100 mg/ml VEGF trap. EX1006, 10:17-20; EX1004, ¶104. The liquid formulation also included 20 mM histidine, 3% PEG 3350, 5% sucrose, and 1.5% glycine at pH 6.3. EX1006, 10:24-26; EX1004, ¶104. In Example 5, another lyophilized formulation was reconstituted into a liquid formulation having 100 mg/ml VEGF trap. EX1006, 10:60-11:1; EX1004, ¶106. The formulation also included 20 mM

histidine, 3% PEG 3350, 5% sucrose, and 1.5% glycine. EX1006, 10:66-11:1; EX1004, ¶106.

C. Vitti (EX1007)

Vitti, a Regeneron patent application titled "Methods and Formulations for Treating Vascular Eye Diseases," published on May 26, 2016, as U.S. Publication 2016/0144025 A1. EX1007, codes [10], [43], [54]; EX1004, ¶85; EX1003, ¶126. Vitti is prior art under 35 U.S.C. §§102(a)(1) and (a)(2).

Vitti is directed to methods for treating vascular eye diseases. EX1007, ¶8; EX1004, ¶86; EX1003, ¶127. Vitti recognizes aflibercept is the "standard of care treatment" for neovascular AMD and DME, and that DME "is a manifestation of DR." EX1007, ¶¶4, 6; EX1003, ¶127-128. Vitti explored potential "synergistic activity to treat" eye disorders including diabetic retinopathy (DR), DME, and AMD (*id*., ¶90) using anti-VEGF (e.g., aflibercept) "in combination with" another compound called angiopoietin-2 (Ang-2) inhibitor. EX1007, ¶¶2, 22, 88, 90; EX1004, ¶87; EX1003, ¶128. Vitti teaches that the formulations may be administered as a single combined-dosage form, EX1007, ¶50, or as separate dosage forms (e.g., where the Ang-2 inhibitor and the VEGF antagonist are "in [their] own separate pharmaceutical dosage formulation" and the VEGF antagonist is "administered before, after or concurrently with the Ang-2 inhibitor"), *id.*, ¶¶50, 91; EX1004, ¶87; EX1003, ¶128. Either way, Vitti teaches the compositions are a stable

liquid form and may be administered intravitreally. EX1007, ¶¶16, 26; EX1003, ¶128.

Vitti teaches that aflibercept may be provided in a pre-filled syringe in a volume of approximately up to 100 µL. *Id.*, ¶¶40, 41, 127; EX1004, ¶88; EX1003, ¶132. Vitti teaches the protein concentration of the VEGF antagonist (aflibercept) is between "5 mg/mL±0.75 mg/mL to about 100 mg/mL±15 mg/mL." EX1007, ¶27; EX1004, ¶88; EX1003, ¶130. Vitti teaches the dose can include "0.05 mg to about 10 mg of a VEGF antagonist (e.g., aflibercept)." *Id.*, ¶139; EX1004, ¶88; EX1003, ¶134. Vitti teaches that "[e]xemplary formulations comprising a VEGF antagonist that can be used in the context of the present invention are disclosed," for example, in ***Furfine***. EX1007, ¶107 (citing EX1005); EX1004, ¶89; EX1003, ¶130.

D. AU EYLEA Label (EX1009)

The AU EYLEA Label ("Label") was publicly available as of at least March 8, 2017. EX1009, 36; EX1065. The Label is prior art under 35 U.S.C. §102(a)(1).

The Label provides product information for EYLEA. EX1009, 29, 35; EX1003, ¶¶135-138. EYLEA is indicated to treat "neovascular (wet) age-related macular degeneration (wet AMD)," "macular oedema following central retinal vein occlusion (CRVO)," and "diabetic macular oedema (DME)." EX1009, 24; EX1003, ¶137. The Label includes clinical trial data from VIVID and VISTA on the efficacy and safety of two dosing regimens of aflibercept, administered intravitreally in

patients with DME. The Label teaches that patients "experienced an improvement in the severity of diabetic retinopathy, as measured by a ≥ 2 step improvement in the diabetic retinopathy severity scale (DRSS)." EX1009, 21; EX1003, ¶137; *see also* EX1016, 2044. The Early Treatment Diabetic Retinopathy Study ("EDTRS") scale and the Diabetic Retinopathy Severity Scale ("DRSS") reflect treatment of different severities of DR, including proliferative and non-proliferative. EX1009, 20, 21; EX1003, ¶137. The Label also references data from patients with "proliferative retinopathy." EX1009, 25; EX1003, ¶137.

The Label states EYLEA is administered intravitreally using a 30-gauge injection needle. EX1009, 31 ("For the intravitreal injection a 30 G x ½ inch injection needle should be used."); EX1003, ¶137.

In a section labeled "OVERDOSAGE," the Label teaches, in clinical trials of EYLEA, "doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8mg were generally well tolerated." EX1009, 35; EX1003, ¶¶60-63, 138. The Label teaches no adverse effects due to the 8mg dose. EX1009, 35; EX1003, ¶138. The only concern the Label identified with these overdoses was due to the "increased injection volume" associated with these doses, which "increased interocular pressure." EX1009, 35; EX1003, ¶138. Thus, the Label teaches, "in case of overdosage[,] intraocular pressure should be monitored," and if necessary further treatment initiated. EX1009, 35; EX1003, ¶138. Tellingly, Regeneron itself has

relied on this "overdose" data to justify its EYLEA HD, 8mg aflibercept indication. EX1066, 19.

E. 2011 EYLEA Clinical Review (EX1008)

The 2011 EYLEA Clinical Review ("Clinical Review") was publicly available as of at least January 18, 2017. EX1008; EX1065. The Clinical Review is prior art under 35 U.S.C. §102(a)(1).

The Clinical Review provides pharmacological and biopharmaceutical findings from several EYLEA clinical trials. EX1008, 2-3; EX1003, ¶158. The Clinical Review discloses that, following intravitreal administration, "aflibercept was not observed to cause increases in DBP [diastolic blood pressure] or SBP [systolic blood pressure]." EX1008, 10-11; EX1003, ¶159.

F. Larson (EX1010)

Larson, titled "Liquid Protein Formulations Containing Water Soluble Organic Dyes," published on March 12, 2015, as U.S. Patent Publication 2015/0071920 A1. EX1010, codes [10], [43], [54]; EX1004, ¶90; EX1003, ¶139. Larson is prior art under 35 U.S.C. §§102(a)(1) and (a)(2).

Larson states that "an object of the present invention [is] to provide low-viscosity liquid formulations of pharmaceutically important proteins, especially high-molecular-weight proteins," that can "improve injectability and/or patient compliance, convenience, and comfort." EX1010, ¶¶16-18; EX1004, ¶¶91-92;

EX1003, ¶140. These high-concentration, low-viscosity liquid formulations have protein concentrations "between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL." EX1010, ¶22; EX1004, ¶93; EX1003, ¶141.

Larson teaches that its formulations are administered "using an 18-32 gauge needle," that "[p]referred needle gauges for the delivery of the low-viscosity formulations include 27, 29, and 31 gauge, optionally thin walled," and contemplates administration via "subcutaneous, intramuscular, or other types of injection." EX1010, ¶¶79, 224, 234; EX1004, ¶96; EX1003, ¶142.

Larson teaches "preparation of formulations having a viscosity less than or about 100 cP…most preferably less than or about 10 cP, when measured at 25° C." EX1010, ¶¶75, 77; EX1004, ¶94; EX1003, ¶143. Larson teaches that "[a]ny protein can be formulated," including "high-molecular-weight proteins" defined as over 100 kDa. EX1010, code [57], ¶¶89, 27; EX1004, ¶95; EX1003, ¶140. "The protein can be…a fusion protein." EX1010, ¶161; EX1004, ¶95; EX1003, ¶140. Larson also identifies EYLEA (aflibercept), "a recombinant fusion protein…formulated as an iso-osmotic solution for intravitreal administration," as a suitable protein for its disclosed formulations. EX1010, ¶¶161, 167; EX1004, ¶95; EX1003, ¶140.

While Larson's patent is directed to a specific way of reducing viscosity, its teachings broadly inform a POSA of target viscosities for injected high-

concentration protein formulations. EX1004, ¶¶50-70, 127, 198; EX1003, ¶144. Petitioner is relying on Larson for this broad teaching. In fact, the challenged '036 patent does not claim any specifics regarding how to achieve the claimed viscosity.

G. Fiedler (EX1011)

Fiedler, titled "Pre-Filled Plastic Syringe Containing a VEGF Antagonist," published on August 17, 2017, as U.S. Patent Publication 2017/0232199 A1. EX1011, codes [10], [43], [54]; EX1004, ¶107; EX1003, ¶154. Fiedler is prior art at least under 35 U.S.C. §102(a)(2). The '036 patent incorporates Fiedler by reference "for all purposes." EX1001, 32:61-64.

Fiedler teaches a pre-filled plastic syringe containing a liquid formulation of anti-VEGF, e.g., aflibercept. EX1011, ¶¶17-18; EX1004, ¶108. Fiedler teaches intravitreal administration of aflibercept to patients suffering from ocular diseases. EX1011, [57], ¶83; EX1004, ¶110; EX1003, ¶¶155-160. Fiedler teaches volume in a pre-filled syringe administered to a patient is between 0.01 and 1 ml (preferably 0.03 to 1 ml), and VEGF antagonist concentration is between 1 to 100 mg/ml. EX1011, ¶¶19, 29, 67; EX1004, ¶¶109, 112 EX1003, ¶¶155-156. Fiedler teaches that "[f]or intravitreal administration the needle size is typically 30 gauge, although 31-, 32, 33- and 34-gauge needles may also be used." EX1011, ¶83; EX1004, ¶111; EX1003, ¶157.

VIII. GROUND 1: CLAIMS 1 AND 4-38 ARE UNPATENTABLE FOR

OBVIOUSNESS OVER VITTI, AU EYLEA LABEL, AND LARSON

High-concentration VEGF antagonist formulations would have been obvious based on the combination of Regeneron's prior disclosures (Vitti and Label), in view of Larson. The combination teaches every limitation of claims 1, 4-38. A POSA would have been motivated to combine the teachings of these references, with a reasonable expectation of success. EX1003, ¶¶161-186.

A. A POSA Would Have Been Motivated to Treat Angiogenic Eye Disorders with High-Concentration VEGF Antagonist Formulations Based on Regeneron's Prior Disclosures and Larson

High-concentration VEGF antagonist formulations (≥100 mg/ml) for treating angiogenic eye disorders were known in the art. Regeneron's patent application, Vitti, teaches "a stable liquid pharmaceutical formulation" that comprises "from 10±1.5 mg/mL to 100 ±15.0 mg/mL of a VEGF antagonist," and further identifies aflibercept as "an example of a VEGF antagonist" for its formulation. EX1007, ¶¶22, 87.

A POSA would have been motivated to treat angiogenic eye disorders with high-concentration VEGF antagonist. EX1003, ¶¶161-186. A POSA would understand that VEGF antagonist concentration dictates the VEGF antagonist dose that can be delivered, so a higher concentration would allow clinicians to treat patients with a correspondingly higher dose of VEGF antagonist. EX1003, ¶165. Treating patients with higher VEGF antagonist doses was desirable because it was

known to have many patient benefits. EX1003, ¶¶161-166.

As D'Amico explains, many patients undergoing traditional VEGF antagonist treatment—monthly injections of 2mg VEGF antagonist—"face[d] considerable logistical, emotional, and financial burdens." EX1003, ¶¶74-76, 162. These burdens led to patients skipping intravitreal injections and/or quitting treatment over time, causing their angiogenic eye disorders to worsen. EX1003, ¶¶74-77, 162-163. Further, frequent injections involved a small but significant risk of blinding and endophthalmitis (a serious inflammation of the intraocular fluids). EX1003, ¶77. A POSA would have recognized that reducing the frequency of injections would ameliorate patient burdens and decrease risks and would thus have explored ways to accomplish this reduction. EX1003, ¶¶78-88. A POSA would also have understood that higher doses of VEGF antagonists correspond to increased duration of action in the eye, which allows for less frequent injections. EX1003, ¶¶84-88, 165-167; EX1039, 1182. A POSA thus have been motivated to increase VEGF antagonist concentration (and correspondingly, VEGF antagonist dose) to realize the benefits associated with less frequent injections. EX1003, ¶¶74-79, 84-88, 161-169.

Given these known motivations, it's not surprising that Regeneron's own prior art discloses higher-concentration and higher-dose VEGF-antagonist formulations. In Vitti, Regeneron disclosed, on the high end, aflibercept concentrations up to 100±15 mg/mL (i.e., 85 mg/mL to 115 mg/mL) and doses of aflibercept up to "about

10mg." EX1007, ¶¶27, 127; EX1003, ¶¶ 130, 180. A POSA seeking to maximize patient benefits would have been motivated to look to these high-end disclosures. EX1007, ¶¶27, 127; EX1003, ¶¶169-180.

A POSA would also have been motivated to combine Vitti's teachings with Regeneron's other disclosures, specifically the Label, because it teaches administering aflibercept formulations like those described in Vitti to patients. EX1003, ¶¶179, 181. The Label specifically teaches that patients were administered 8mg of aflibercept intravitreally, and this dose was "generally well tolerated" in clinical trials. EX1009, 35; EX1003, ¶¶ 138, 179. While the Label termed these doses "overdoses," the only concern it identifies is that injecting 8mg instead of 2mg (4x the dose) was associated with "increased injection volume" (4x the volume), which in turn "increased interocular pressure." EX1009, 35; EX1003, ¶179. Tellingly, Regeneron itself has relied on this "overdose" data to justify its EYLEA HD, 8mg aflibercept indication. EX1066, 19; EX1003, 64. Further, the prior art taught that a 4-fold increase in dosage of VEGF was safe, effective, and increased the duration of action of the VEGF in the eye. EX1003, ¶169; EX1039, 1182; EX1026, 2182, 2190; EX1035, 586-87; *see also* EX1058, 20-21; EX1030, 14. As such, a POSA would have been motivated to combine the teachings of Vitti and the Label to target an 8mg dose of aflibercept. EX1003, ¶¶165-182.

Similarly, a POSA would have been motivated to combine Vitti and the Label

with Larson because Larson teaches target viscosity ranges for high-concentration protein formulations, like those described in Vitti, that are administered through small gauge needles. EX1003, ¶¶181-85. A POSA would have understood that viscosity is a relevant characteristic to consider in these formulations. EX1004, ¶¶44, 48-49. Regeneron's Label teaches aflibercept was administrated through a 30-gauge needle. EX1009, 31; EX1003, ¶181. This is consistent with the practice in the art, as a 30-gauge needle was a common choice for the intravitreal administration of other anti-VEGF drugs. EX1003, 65-72; EX1011, ¶52; EX1055, §2.1; EX1048, §2.3l. A POSA would have understood that any high-concentration, high-dosage formulation would thus need to have a viscosity suitable for injection through such a 30-gauge needle. EX1003, ¶182. Larson teaches that the "most preferabl[e]" viscosity for high-concentration protein formulations (including formulations containing "greater than 100 mg/mL" protein) administered using a 30-gauge needle is "less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C." EX1010, ¶¶75, 77, 167, 231; EX1003, ¶¶183-185. Larson further references EYLEA. EX1003, ¶184; EX1010, ¶167.

A POSA would have been motivated to combine Vitti, the Label, and Larson to achieve the claimed high-concentration, high-dose formulation with a viscosity suitable for intravitreal administration of high-concentration formulations for VEGF antagonists like aflibercept. EX1003, ¶186.

B. A POSA Would Have Had a Reasonable Expectation of Success in Creating a High-Concentration VEGF Antagonist Formulation

A POSA would have had a reasonable expectation of success in achieving the claimed invention. Vitti teaches a stable liquid formulation for intravitreal administration of aflibercept to treat angiogenic eye disorders using high concentrations up to 115 mg/mL of aflibercept using doses of up to 10 mg aflibercept at injection volumes up to 100 μL. EX1003, ¶¶ 130-134, 165, 180; EX1004, ¶¶114-118; EX1007, ¶139. Vitti thus teaches a reasonable expectation of success in treating a patient with the claimed vascular eye diseases, including DR, DME, and AMD, by intravitreally administrating VEGF antagonist formulations at the claimed concentration and dosage ranges. EX1003, ¶186.

Other teachings in the art further support reasonable expectation of success. It was known that aflibercept acts as a decoy receptor or "VEGF-trap," meaning in simple terms it binds excess VEGF produced by the eye. EX1003, ¶¶39-40, 171. A POSA would have expected higher-dose aflibercept to have a longer duration of action in the eye (i.e., durability) and lay in wait in the eye to bind the patient's ongoing production of VEGF. EX1003, ¶172; EX1039, 1182. The prior art taught just that: a study regarding aflibercept and another anti-VEGF drug, ranibizumab, reported that a 4-fold increase in dose "has a greater effect on its durability than its efficacy," meaning that high concentrations of VEGF antagonist would increase the

duration of action in the eye (i.e., trapping VEGF) without reducing its ability to treat angiogenic eye disorders. EX1003, ¶172; EX1039, 1182; EX1026, 2182, 2190.

The CLEAR-IT study reported in Nguyen 2012 similarly showed that the safety and tolerability of 0.15mg and 4mg doses of aflibercept were identical, and it noted that the "higher dose of intravitreal aflibercept may have increased bioactivity, but did not carry additional risks of deleterious effects." EX1035, 586-87; EX1003, ¶167. Still other studies demonstrated intravitreal doses of aflibercept did not pose a risk of systemic toxicity or other adverse events. EX1003, ¶¶43-58, 179; EX1058, 20-21; EX1030, 14. And, finally, as discussed, the Label teaches that 8mg doses were generally well tolerated. EX1009, 35; EX1003, ¶168. This art further confirms a POSA would have had a reasonable expectation of success in treating angiogenic eye disorders with high concentration, high dose aflibercept formulations. EX1003, ¶¶161-186.

A POSA would also have a reasonable expectation of success in being able to formulate higher-concentration formulations with the claimed viscosity. EX1004, ¶¶119-128. Vitti teaches its formulations are administered intravitreally and does not identify any concern about achieving the desired viscosities for such administration. It thus provides the reasonable expectation that such a formulation has been, or can be, achieved.

Larson supports reasonable expectation of success as well. Larson teaches

that viscosities encompassing the claimed range are suitable for high-concentration protein formulations, including aflibercept formulations. EX1010, ¶¶75, 167; EX1004, ¶123. It further teaches that such formulations are administered intravitreally through an 18-32 gauge needle (which encompasses the 30-gauge needle taught in the Label). EX1010, ¶¶49; EX1009, 31; EX1004, ¶123. A POSA reading Larson would thus have a reasonable expectation of success in creating a formulation with the claimed concentration and viscosity. EX1004, ¶¶119-128.

Other teachings in the art are consistent. Furfine, another Regeneron publication, teaches ophthalmic formulations comprising of up to 100 mg/ml VEGF antagonist can be "provided in a pre-filled syringe or vial, ***particularly suitable for intravitreal injection***."[2] EX1005, 2:4:65-67; *see also id.*, 19:31-34 (claim 1 reciting an ophthalmic formulation comprising 1-100 mg/ml of a VEGF antagonist). And Dix teaches that "high concentration" VEGF antagonist formulations—*e.g.*, 100 mg/ml—can be made into stable liquid formulations. EX1006, 2:20-24. Vitti points to Furfine for representative formulations. EX1007, ¶107.

To the extent Vitti's formulation needed to be modified to have a lower viscosity, a skilled artisan would have a reasonable expectation of success in making such a modification. EX1004, ¶127. Larson teaches one way to reduce viscosity

[2] Emphasis added throughout unless otherwise indicated.

(using organic dyes), but a POSA would have been well aware of other ways—such as the use of a viscosity reducing agent or other excipients "added to the formulation to provide a desired consistency, viscosity, or stabilizing effect." EX1007, ¶96; EX1004, ¶¶52-70, 127. And nothing in the '036 patent claims recite a specific solution to a viscosity problem. *See infra*, §X.A-B. (showing lack of written description for all claims).

Thus, a POSA would have had a reasonable expectation of success in achieving a formulation consistent with the claimed method of treatment. EX1003, ¶186.

C. Claim 1

1[A] *A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject*

To the extent the preamble is limiting, Regeneron's prior disclosures teach it. EX1003, ¶¶187-191. Vitti teaches that "[a]nti-vascular endothelial growth factor (VEGF) therapy (e.g., aflibercept) is the standard of care treatment for neovascular" AMD and DME. EX1007, ¶6. Vitti further teaches that vascular eye diseases, such as AMD and DME, are "eye disease[s] or disorder[s] associated with angiogenesis." *Id.*, ¶53. Vitti also provides evidence that intravitreal administration of aflibercept was well known in the art. *See id.*, ¶7 ("Intravitreal (IVT) deliveries of anti-VEGF therapies such as ranibizumab and aflibercept have demonstrated efficacy and safety

for chorioretinal diseases."). In one embodiment, Vitti teaches a method for treating an angiogenic eye disorder "compris[ing] administering a single dose of a VEGF antagonist followed by one or more doses" of Ang-2 inhibitor. *Id.*, ¶12.

The Label also teaches treating wet AMD, DME, and visual impairment due to macular oedema secondary to CRVO in humans—all well known as angiogenic eye disorders—via intravitreal injection of aflibercept into the eye. EX1009, 24, 29-30; EX1003, ¶191.

1[B] *in a volume of about 100 microliters or less*

Regeneron's prior disclosures teach this limitation. EX1003, ¶¶192-194. Vitti teaches the pharmaceutical formulations may be provided in a pre-filled syringe and "administered intravitreally in a volume of approximately upto [*sic*] 100 µL." EX1007, ¶127. As D'Amico explains, a POSA would understand the acceptable volume for intravitreal injections ranged from 20 µL to 100 µL. EX1003, ¶193. At the relevant time, there were four anti-VEGF products on the market—three were 50 µL injections and one was a 90 µL injection. EX1003, ¶¶71-72, 193.

1[C] *at least about 8 mg*

Regeneron's prior disclosures teach this limitation. EX1003, ¶¶195-198. First, Vitti teaches its formulations can include "0.05 mg to about 10 mg of a VEGF antagonist (e.g., aflibercept)." EX1007, ¶139. Vitti thus discloses formulations with "at least about 8 mg" of aflibercept, as claimed. At a minimum, Vitti's disclosed

range overlaps with the unbounded range of "at least 8 mg," and thus renders this limitation *prima facie* obvious. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (applying a presumption of obviousness because of overlapping ranges); *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022) (same).

Second, as D'Amico explains, a POSA would have also understood Vitti discloses "at least about 8 mg" through its description of protein concentration and volume of preferred embodiments. EX1003, ¶¶196-197. Vitti teaches, in certain embodiments, the pharmaceutical formulations contain "5±0.75 mg/mL to 100±15 mg/mL of a VEGF antagonist." EX1007, ¶94. Vitti also expressly discloses embodiments of "about 80 mg/ml," "about 90 mg/ml," and "about 100 mg/mL" of a "VEGF antagonist such as aflibercept." *Id.*

Combined with Vitti's teaching of using a volume up to 100 microliters (*supra*, §VIII.A.), a POSA would have employed basic and routine mathematics to calculate the amount (in mg) of aflibercept in each of Vitti's embodiments. EX1003, ¶197. Vitti's "about 80 mg/ml" embodiment, for example, contains "about 8 mg" aflibercept in a volume of 100 µl (80 mg/ml x 0.1 ml=8 mg). Vitti's "about 90 mg/ml" embodiment contains "about 9 mg" aflibercept. And Vitti's "about 100 mg/ml" embodiment contains "about 10 mg" aflibercept. *Id*. Because Vitti teaches 8mg, 9mg, and 10mg doses of aflibercept, it teaches, or at least renders *prima facie*

obvious, the limitation of "at least about 8 mg." *E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272.

Third, the Label also discloses that, in clinical trials of EYLEA, some patients received 8mg aflibercept and those were "***generally well tolerated***." EX1009, 35. While the Label termed these 8mg doses "overdoses" (because the indicated treatment was 2mg), the Label does not suggest the 8mg dose itself caused any concerns with efficacy or safety. EX1003, ¶198. Indeed, the only concern it identifies is increased interocular pressure from the "increased injection volume" associated with quadrupling the 2mg dose (at 50 microliters) to 8mg (which would be a volume of 200 microliters). *Id*.

Thus, the Label expressly teaches "at least about 8 mg." EX1003, ¶198; *see Recor Med., Inc. v. Medtronic Ireland Mfg. Unlimited Co.*, No. 2023-2251, 2025 WL 944511, at *2 (Fed. Cir. Mar. 27, 2025) ("[A] reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect.") (quoting *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985)).

1[D] *of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component*

Regeneron's prior disclosures are all directed to pharmaceutical formulations comprising VEGF antagonist, which meets this claim limitation. EX1003, ¶¶199-

203; *supra*, §II.

Vitti discloses that a VEGF antagonist "comprise[s] two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also referred to as Flt1) and/or VEGFR2 (also referred to as Flk1 or KDR), and may also contain a multimerizing domain (e.g., an Fc domain which facilitates the multimerization [e.g., dimerization] of two or more chimeric polypeptides)." EX1007, ¶86. Vitti also exemplifies VEGFR1R2-FcΔC1(a) as a specific VEGF antagonist known as aflibercept and marketed as EYLEA. *Id.;* EX1003, 129. The Label also discloses aflibercept. EX1009, 1-2.

As D'Amico testifies, a POSA would recognize these descriptions from the prior art as describing the same fusion protein claimed. EX1003, ¶203.

The '036 patent, like Vitti, contemplates combinations of the aflibercept formulation with Ang-2 inhibitors and, given the "comprising" language of the claims, would cover such a combination. EX1001, 15:7-20, claim 1.

1[E] *wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein*

Regeneron's prior disclosures teach this limitation. EX1003, ¶¶204-207; EX1004, ¶¶114-118.

Vitti teaches a "stable liquid pharmaceutical formulation" comprising VEGF antagonist. EX1007, ¶26. Vitti teaches that the formulation may be "an aqueous

solution…for IVT [intravitreal] administration." EX1007, ¶260. Vitti also teaches the formulation may comprise "10±1.5 mg/mL to 100±15.0 mg/mL" of VEGF antagonist. *Id.*, ¶87; *see also id.*, ¶94. Vitti thus teaches formulations ranging up to 115 mg/mL, which is "at least 100 mg/mL" of VEGF antagonist.

Moreover, as discussed above, a POSA would have been motivated to look at the high end of Vitti's disclosure, which is a range of 100±15.0 mg/mL (i.e., 85 mg/mL to 115 mg/mL). EX1003, ¶¶161-180, 206; *supra*, §VIII.A. Because this range overlaps with the claimed unbounded range of "at least 100 mg/mL," Vitti renders this limitation *prima facie* obvious. *E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272. At a minimum, Vitti's disclosure of "10±1.5 mg/mL to 100±15.0 mg/mL" overlaps with the claimed unbounded range, so this limitation is *prima facie* obvious.

1[F] *and having a viscosity of about 5-15 centiPoise (cP) at 20°C*

Regeneron's prior disclosures in combination with Larson teach this limitation. EX1003, ¶208; EX1004, ¶¶119-128.

Vitti teaches the use of excipients to "provide a desired consistency, viscosity, or stabilizing effect." EX1007, ¶96. Moreover, Vitti teaches its aflibercept formulations are administered intravitreally using a syringe fitted with a 30-gauge needle. *Id.*, ¶¶18, 115, 127. Vitti does not identify any concern with achieving the "desired" viscosities for its intravitreally administered formulations.

Larson further teaches what these "desired" viscosities are for pharmaceutical protein formulations, like the ones disclosed in Vitti. Specifically, Larson teaches the use of viscosity-reducing excipients to obtain aqueous pharmaceutical formulations with a viscosity of "less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C." EX1010, ¶¶75, 77. As Falconer confirms, a POSA would have understood that a protein formulation with a viscosity of 10 cP measured at 25°C would have had a viscosity of approximately 11.26 cP measured at 20°C, and a protein formulation with a viscosity of 20 cP measured at 25°C would have a viscosity of approximately 22.52 cP measured at 20°C. EX1004, ¶124. Larson thus teaches formulations having a viscosity within the claimed ranges. EX1004, ¶124. At a minimum, Larson's disclosed viscosity ranges either overlap with or fully encompass the claimed range, and thus render this limitation obvious. *E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272; *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (*prima facia* obviousness "even more compelling" where "the claimed ranges are completely encompassed by the prior art").

As explained above, a POSA would have looked to Larson's viscosity values because, like Regeneron's prior disclosures, Larson also teaches high-concentration liquid formulations that are administered via injection using 30-gauge needles. *Supra*, §VIII.A.; EX1004, ¶122. Specifically, Larson describes protein concentrations above "about 100 mg/mL to about 2,000 mg/mL." EX1010, ¶22.

Larson also teaches that "[a]ny protein can be formulated" and expressly identifies aflibercept as an example of a protein that can be formulated with viscosity-reducing excipients. *Id.*, ¶¶89, 161, 167. Larson's formulations are administered "using an 18-32 gauge needle," and Larson contemplates administration via "subcutaneous, intramuscular, or other types of injection," which would include intravitreal injection. EX1010, ¶¶224; EX1004, ¶125.

A POSA would have understood from Larson that a VEGF antagonist formulation that is administered intravitreally using a syringe with a 30-gauge needle, as taught in Vitti, would have a desired viscosity of about 5-15 cP at 20°C. EX1010, ¶¶75, 77, 224, 234; EX1004, ¶125. Accordingly, a POSA, in light of Vitti and Larson, would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with a protein concentration of at least 100 mg/mL and a viscosity within the claimed range of about 5-15 cP at 20°C. EX1004, ¶¶119-128.

Moreover, as Falconer explains, there were several formulation strategies known and available to a POSA that had already been successfully applied to improve the viscosity characteristics of high-concentration protein formulations, including (a) adding amino acids; (b) adding salts; (c) minimizing the use of sugars or sugar alcohols; (d) adjusting pH relative to pI of the protein; (e) adding viscosity-lowering water soluble dyes; and (f) emulsification. EX1004, ¶¶52-70, 127. A

POSA would therefore have understood, with a reasonable expectation of success, that any one of a number of available solutions in the art could have been applied to an aqueous pharmaceutical formulation containing at least 100 mg/mL of aflibercept, as taught in Vitti, to achieve the viscosity of about 5-15 cP at 20°C taught in Larson. EX1004, ¶127.

Fundamentally, the claimed viscosity range is merely the work of "routine optimization" and thus obvious. *See Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347 (Fed. Cir. 2024); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (obvious to optimize formulation variables).

D. Claims 4-34

1. Claims 4-8

Claims 4-8 depend from claim 1 and each recite various viscosities in cP at 20ºC ("about 10-13 cP," "about 11-12 cP," "about 12-15 cP," "about 5 cP" and "about 6 cP"). EX1001, 62:52-61. Regeneron's prior disclosures in combination with Larson teach these limitations. EX1003, ¶¶209-212; EX1004, ¶¶129-143.

As discussed above, a POSA would have understood that Larson's teaching of a viscosity of "less than or about 20 cP" (EX1010, ¶¶75, 77) is approximately equivalent to less than or about 22.52 cP at 20°C. EX1004, ¶¶124, 129-143. A POSA would have also understood that Larson's teaching of a viscosity of "less than or about 10 cP, when measured at 25° C" (EX1010, ¶¶75, 77) is approximately

equivalent to less than or about 11.26 cP at 20°C. EX1004, ¶¶124, 129-143. Because Larson's viscosity ranges encompass the claimed viscosity ranges and values, Larson renders these claims *prima facie* obvious. *E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272; *see also Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (applying presumption of obviousness where prior art disclosed a range that encompassed claimed value); *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 141 F.4th 1367, 1375 (Fed. Cir. 2025) (overlapping ranges presumption has applied in cases where the claim "requires a feature in a numerical amount (specified as, *e.g.*, a single figure or a range)" and the prior art teaches a range that "overlap[s] with the claimed numerical amount").

2. Claims 9, 10

Claims 9 and 10 depend from claim 1. EX1001, 62:62-66. Claim 9 recites that the formulation comprises "a sugar," and claim 10 recites that the formulation comprises "sucrose, trehalose, sorbitol, mannitol, propane sulfonic acid or glycerol." *Id.* Regeneron's prior disclosures teach these limitations. EX1003, ¶¶213-216; EX1004, ¶¶144-147. Vitti teaches the addition of a sugar, such as sucrose, to its pharmaceutical formulations. EX1007, ¶33. Vitti also directs a POSA to Furfine (EX1005) for "[e]xemplary formulations comprising a VEGF antagonist." *Id.*, ¶107. Furfine, in turn, teaches that the ophthalmic formulation optionally comprises a stabilizing agent that may be sucrose. EX1005, 2:15-16.

Claim 10 recites specific sugars in the alternative (using "or"). The disclosure of one sugar in the prior art—sucrose—renders this limitation obvious. *See In re Klein*, 987 F.2d 1569, 1570 (Fed. Cir. 1993) (where a "single claim covers plural alternative embodiments…the §103 rejection is proper if the prior art demonstrates the obviousness of any one of them"); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015).

3. Claim 11

Claim 11 depends from 1 and recites that the formulation "comprises an amino acid." EX1001, 63:1-2. Regeneron's prior disclosures and Larson teach this limitation. EX1003, ¶¶216-218; EX1004, ¶¶148-149. Vitti discloses its pharmaceutical formulations may comprise "excipients" to "provide a desired consistency, viscosity or stabilizing effect." EX1007, ¶96. Vitti discloses a "buffer or buffer system" as one such excipient. *Id.*, ¶106. Larson discloses the use of "L-histidine buffer" in commercial therapeutic protein products, which includes L-histidine, an amino acid. EX1010, ¶8. As additional evidence of the common use of amino acids in pharmaceutical formulations, Dix confirms histidine was suitable for use in a formulation comprising aflibercept. EX1006, 10:14-11:1, 19:37-42, 20:37-41. Thus, the teachings of Vitti in view of Larson renders this limitation obvious. EX1003, ¶¶217-219.

4. Claim 12

Claim 12 depends from claim 1 and recites that "the VEGF receptor fusion protein is aflibercept." EX1001, 63:3-4. Regeneron's prior disclosures teach this limitation. EX1003, ¶¶219-220; EX1004, ¶150. Vitti teaches an exemplary VEGF antagonist is aflibercept. EX1007, ¶86. The Label also teaches the VEGF antagonist is aflibercept. EX1009, 1-2.

5. Claims 13-26

Claim 13 depends from claim 1 and recites a genus of angiogenic eye disorders in the alternative by using the disjunctive "and/or." EX1001, 63:5-17; *see Cochlear Bone Anchored Sols. AB v. Oticon Med. AB*, 958 F.3d 1348, 1359 (Fed. Cir. 2020) (use of the disjunctive "and/or" creates "alternative subsets of claim coverage"); *Klein*, 987 F.2d at 1570. Claims 14, 16, 18, 20, 22, and 24 all separately claim individual angiogenic eye diseases. All these claims are rendered obvious by Regeneron's prior disclosures. EX1003, ¶¶221-243; EX1004, ¶¶151-164.

The use of aflibercept for treating several angiogenic eye disorders was known. EX1003, ¶¶189-191, 223. The Label indicates aflibercept in adults for the treatment of neovascular wet AMD (**claim 14**), visual impairment due to macular oedema secondary to CRVO (**claim 24**), and DME (**claim 16**). EX1009, 24; EX1003, ¶¶189-191, 223. Regarding DME, D'Amico explains, "oedema" and "edema" represent alternative spellings. EX1003, ¶¶230, 242.

The Label further discloses that aflibercept treats DR (**claim 18**), including non-prolific DR (**claim 20**) and prolific DR (**claim 22**), as evidenced by its inclusion of VIVID and VISTA clinical trial data. EX1009, 16-21. As D'Amico explains, the Label discusses the treatment of DME, which was well known in the art to be a manifestation, and the major cause, of visual loss associated with DR. EX1003, ¶222. VIVID and VISTA tested the efficacy and safety of two dosing regimens of aflibercept, administered intravitreally in patients with DME. It was observed in these trials, as taught in the Label, that patients "experienced an improvement in the severity of diabetic retinopathy, as measured by a ≥ 2 step improvement in the diabetic retinopathy severity scale (DRSS)." EX1009, 21; *see also* EX1016, 2044. Additionally, the use of the EDTRS (Early Treatment Diabetic Retinopathy Study) scale and the DRSS for assessing efficacy reflect treatment of different severities of DR, including proliferative and non-proliferative. EX1009, 19-21; EX1003, ¶235. The Label also references data from patients with "proliferative retinopathy." EX1009, 25.

Vitti further teaches aflibercept is the "standard of care treatment for neovascular AMD…and DME" (EX1007, ¶6) and later defines "AMD" as encompassing "wet AMD" (*id.*, ¶56). Like the Label, Vitti also teaches DME is a manifestation of DR. *Id*., ¶4.

Claims 15, 17, 19, 21, 23, 25, and 26 depend from claims 14, 16, 18, 20, 22,

24, and 13, respectively, and recite that the VEGF receptor fusion protein is aflibercept. EX1001, 63:24-25. The Label and Vitti, relied on above, both relate to aflibercept and its uses. EX1009, 1-2, 24.

A POSA would have considered it obvious and expected that high-dose aflibercept would treat the same diseases as low-dose aflibercept. EX1003, ¶171.

First, Vitti already discloses high-dose formulations of VEGF antagonist, including up to 115 mg/mL and an embodiment of about 100 mg/ml VEGF antagonist. EX1007, ¶¶87, 94. And Vitti teaches that the "present invention" allows for the treatment of angiogenic eye disorders by administering a single dose of a VEGF antagonist followed by one or more doses of a pharmaceutical formulation comprising Ang-2 inhibitor. *Id.*, ¶12. Taken together, these disclosures teach a POSA that high-dose formulations of VEGF antagonist would have treated angiogenic eye disorders like AMD and DME. EX1003, ¶171.

That Vitti teaches the additional step of treating with Ang-2 following treatment with VEGF antagonist does not negate Vitti's teachings. Claim 1 recites "comprising" and therefore does not exclude additional steps. *See, e.g.*, *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003). The '036 patent in fact contemplates formulations that include aflibercept with an ang-2 inhibitor. EX1001, 15:19. Even so, Vitti refers to the "additive or synergistic activity" between the two components, teaching that aflibercept treats the diseases independently,

recognizing it is the "standard of care treatment for neovascular AMD and DME." EX1007, ¶¶9, 238.

Second, D'Amico explains that a POSA would thus have expected a high-concentration (high-dose) aflibercept formulation to be at least as efficacious for treating angiogenic eye disorders, including AMD, DME, and DR, as low-concentration (low-dose) EYLEA. EX 1003, ¶171. This is exemplified by the results of the CLEAR-IT study (comparing 0.05mg to 4mg), the tolerability of the 8mg dose described in the Label, and the field's understanding how increasing the dose would increase aflibercept's duration of action without negatively impacting efficacy. EX1035, 586-587; EX1009, 35; EX1039 at 1182. The CLEAR-IT study, for example, showed that higher doses of intravitreal aflibercept "did not carry additional risks of deleterious effects." EX1035, 586-87; EX1003, ¶167; *supra*, §VIII.B.

6. Claim 27

Claim 27 depends from claim 1. EX1001, 62:3-9. Claim 27 is identical to claim 1 except that it narrows the protein concentration limitation from "at least 8 mg of a VEGF receptor fusion protein" to "about 8 mg aflibercept." *Id.*, 62:6-7. Regeneron's prior disclosures teach this limitation for the reasons explained above in limitations 1[C] and 1[D] and claim 12. *Supra*, §§VII.C.1[C]-1[D], §VIII.D.4; EX1003, ¶¶244-245; EX1004, ¶165. Moreover, Vitti's disclosed range of "0.05 mg

to about 10 mg of a VEGF antagonist (e.g., aflibercept)" renders "about 8 mg aflibercept" *prima facie* obvious. EX1007, ¶139; *see Galderma*, 737 F.3d at 738.

7. Claims 28-30

Claims 28-30 depend from claim 27 and recite various angiogenic eye disorders. EX1001, 64:10-13. Regeneron's prior disclosures teach, or at the very least, render this limitation obvious, for the reasons explained above in claims 13, 14, 16, and 18. *Supra*, §VIII.D.5; EX1004, ¶¶166-168. Specifically, the Label teaches all these angiogenic eye disorders can be treated with aflibercept. EX1003, ¶¶246-249; EX1009, 8-25; *see also* EX1016, 2044.

As D'Amico explains, a POSA would have understood and recognized that a higher-concentration formulation (i.e., 114.3 mg/ml) of aflibercept would treat the same diseases as the lower-concentration formulation, for the reasons also explained above. *Supra*, §VIII.D.5.

8. Claim 31

Claim 31 depends from claim 1. EX1001, 64:16-22. Claim 31 is identical to claim 1 except that it: (1) narrows the volume limitation from "about 100 microliters or less" to "about 70 microliters," (2) narrows the dose limitation from "at least 8 mg of a VEGF receptor fusion protein" to "about 8 mg aflibercept," and (3) narrows the protein concentration limitation from "at least 100 mg/ml" to "about 114.3 mg/ml." *Id.* Regeneron's prior disclosures in combination with Larson teach these

limitations. EX1003 ¶¶250-254, EX1004, ¶¶240-253.

As to "about 8 mg aflibercept," Regeneron's prior disclosures teach, or at least render obvious, this limitation, for the reasons explained above in limitations 1[C], 1[D], and claim 27. *Supra*, §§VII.C.1[C]-1[D], VIII.D.6.

Vitti teaches the formulation may comprise "10±1.5 mg/mL to 100±15.0 mg/mL" of VEGF antagonist. EX1007, ¶¶87, 94. As discussed above, a POSA would have been motivated to look at the high end of Vitti's disclosure, which is a range of 100±15.0 mg/mL (i.e., 85 mg/mL to 115 mg/mL). *Supra*, §VIII.A.; EX1003, ¶169. Because the claimed concentration of "about 114.3 mg/ml" falls within this range, Vitti renders the limitation *prima facie* obvious. *Galderma*, 737 F.3d at 738. At a minimum, the claimed concentration falls with Vitti's disclosure of "10±1.5 mg/mL to 100±15.0 mg/mL" and is thus *prima facie* obvious for that reason.

Moreover, Vitti teaches that its high-concentration pharmaceutical formulations, which contain up to 115 mg/mL of aflibercept, may be administered intravitreally. EX1007, ¶¶94, 127. Vitti also teaches that its formulations "typically exhibit high levels of stability." *Id.*, ¶108. Vitti therefore confirms a skilled artisan would have reasonably expected to succeed in obtaining a formulation containing up to 115 mg/mL of aflibercept that is stable and suitable for intravitreal administration. EX1004, ¶¶169-172. A POSA also would have been aware of the

trend towards higher-concentration therapeutic protein formulations and the numerous successfully developed high-concentration therapeutic protein formulations already FDA-approved and commercially available at the time, further confirming the expectation of success. EX1004, ¶¶43, 173.

Given the teachings in Vitti regarding stable aqueous pharmaceutical formulations for intravitreal injection containing up to 115 mg/mL of aflibercept (EX1007, ¶¶94, 108, 127), a POSA would reasonably expect that an aqueous pharmaceutical formulation containing about 114.3 mg/mL would likewise be stable and suitable for intravitreal administration. EX1004, ¶172.

Vitti teaches its formulations are "administered intravitreally in a volume of approximately upto [*sic*] 100 μL." EX1007, ¶127. The claimed volume falls within Vitti's disclosed range, so Vitti renders the limitation *prima facie* obvious. *Galderma*, 737 F.3d at 738. Moreover, as Falconer explains, concentration is an expression of the amount of the solute (i.e., dose) present per unit of total volume of the solution. EX1004, ¶176. Thus, within the parameters described above—an 8mg dose of aflibercept provided in a concentration of approximately 114.3 mg/ml—a POSA would have been able to determine the appropriate injection volume to be approximately 70 μL. EX1004, ¶¶174-177. This limitation merely reflects "routine optimization" and is thus obvious. *Pfizer*, 94 F.4th at 1347; *Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 34 (Fed. Cir. 2020) (reversing summary

judgment of no obviousness where there were a finite number of options from which a POSA could choose for a formulation); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d at 1368.

Dose (mg)	Injection Volume (µL)	Concentration (mg/mL)
8	50	160
8	60	133.3
8	**70**	**114.3**
8	80	100
8	90	88.9
8	100	80

In light of Vitti, a POSA would have reasonably expected to succeed in obtaining an aqueous pharmaceutical formulation for intravitreal administration with about 114.3 mg/mL of aflibercept allowing for delivery of an 8mg dose in 70 µL. EX1004, ¶¶169-178.

9. Claims 32-34

Claims 32-34 depend from claim 31 and recite various angiogenic eye disorders. EX1001, 64:23-28.

Regeneron's prior disclosures teach the limitations of these claims for the same reasons they teach claims 14, 16, and 18, discussed above. *Supra*, §VIII.D.5; EX1003, ¶¶255-256; EX1004, ¶¶179-181. As D'Amico explains, a POSA would have understood and recognized a higher-concentration formulation (i.e., 114.3 mg/ml) of aflibercept would treat the same diseases as the lower-concentration formulation, for the reasons also explained above. *Supra*, §VIII.D.5.

E. Claim 35

35[A] *A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject*

To the extent the preamble is limiting, Regeneron's prior disclosures teach it for the same reasons that they teach limitation 1[A], as explained above. *Supra*, §VIII.C.1[A]; EX1003, ¶¶187-191, 257-259.

35[B] *about 70 microliters*

Regeneron's prior disclosure renders this limitation obvious for the reasons discussed above in claim 31. *Supra*, §VIII.D.8.; EX1003, ¶260.

35[C] *of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept*

Vitti renders this limitation obvious. EX1003, ¶¶261-264; EX1004, ¶¶182-185. Vitti teaches a "stable liquid pharmaceutical formulation" comprising the VEGF antagonist aflibercept. EX1007, ¶26. Vitti also teaches the "liquid" formulation may be supplied "as an aqueous solution…for IVT [intravitreal] administration." *Id.*, ¶260. Vitti teaches the formulation may comprise "10±1.5 mg/mL to 100±15.0 mg/mL" of VEGF antagonist. *Id.*, ¶¶87, 94.

As discussed above, a POSA would have been motivated to look at the high end of Vitti's disclosure, which is a range of 100±15.0 mg/mL (i.e., 85 mg/mL to 115 mg/mL). *Supra* §VIII.A. Because this range overlaps with the claimed range, Vitti renders this limitation *prima facie* obvious. *E.I. DuPont*, 904 F.3d at 1008;

Almirall, 28 F.4th at 272. At a minimum, Vitti's disclosure of "10±1.5 mg/mL to 100±15.0 mg/mL" overlaps with the claimed range, so this limitation is *prima facie* obvious.

Moreover, as Falconer explains, it would have been obvious for a POSA to have formulated high-concentration aflibercept in the range of about 103 to 126 mg/ml. EX1004, ¶¶182-185. As discussed above, Vitti teaches high-concentration aqueous pharmaceutical formulations that contain 85 mg/mL to 115 mg/mL of aflibercept, which includes the range of 103 mg/mL to 115 mg/mL. EX1007, ¶94. Vitti's teaching that its formulations containing up to 115 mg/mL of aflibercept "typically exhibit high levels of stability" and may be administered intravitreally (EX1007, ¶¶108, 127) confirms that a skilled formulator would have reasonably expected to succeed in making a stable aflibercept formulation for intravitreal administration with a concentration of up to 115 mg/mL and within the claimed range. EX1004, ¶¶182-185.

35[D] *and having a viscosity of about 5-15 cP at 20°C*

Regeneron's prior disclosures in view of Larson render this limitation obvious for the reasons discussed above in limitation 1[F] and claim 31. *Supra*, §VIII.C.1[F], VIII.D.8; EX1003, ¶¶207, 250-254, 265; EX1004, ¶¶119-128. As Falconer explains, a POSA would have understood that Larson teaches aqueous pharmaceutical protein formulations that have a viscosity of about 5-15 cP at 20°C. *Supra*, § VIII.C.1[F]. A

POSA would have had a reasonable expectation of success of obtaining a viscosity of about 5-15 cP at 20°C for the reasons discussed above in limitation 1[F] and claim 31. *Supra*, §§VIII.C.1[F], VIII.D.8.

F. Claims 36-38

Claims 36-38 depend from claim 35 and recite various angiogenic eye disorders. EX1001, 64:35-40.

Regeneron's prior disclosure teach the limitations of these claims for the same reasons they teach claims 14, 16, and 18, and claims 32-34, discussed above. *Supra*, §§VIII.D.5, VIII.D.9; EX1004, ¶¶186-188. As D'Amico explains, a POSA would have understood and recognized that a higher-concentration formulation of aflibercept (i.e., 103-126 mg/ml) would treat the same diseases as the lower-concentration formulation, for the reasons also explained above. *Supra*, §VIII.D.5; EX1003, ¶266-267.

IX. GROUND 2: CLAIMS 1 AND 4-38 ARE UNPATENTABLE FOR OBVIOUSNESS OVER FURFINE, DIX, AU EYLEA LABEL, AND FIEDLER IN VIEW OF LARSON

A method for treating angiogenic eye disorders with a high-concentration VEGF antagonist formulation would have been obvious to a POSA based on Regeneron's prior disclosures (Furfine, Dix, and Label) and Fiedler in view of Larson. The combination teaches every limitation of claims 1 and 4-38. And, for the reasons explained below, a POSA would have been motivated to combine the

teachings of the prior-art references, with a reasonable expectation of success, to achieve the claimed invention.

A. A POSA Would Have Been Motivated to Treat Angiogenic Eye Disorders with High-Concentration VEGF Antagonist Formulations Based on Regeneron's Prior Disclosures, Fiedler, and Larson

It was well known in the art that low doses of VEGF antagonists—including 2mg and 4mg aflibercept— successfully treated angiogenic eye disorders, but carried a high "treatment burden," discussed in more detail above in Ground 1. EX1003, ¶¶162, 268-271; *supra*, §VIII.A-B. Thus, as discussed above, POSAs were highly motivated to lessen the severity of treatment burden while maintaining the ability of VEGF antagonist to successfully treat angiogenic eye disorders. EX1003, ¶¶162-164, 271. Well before the '036 patent, POSAs determined that a solution to these concerns was to increase the VEGF antagonist concentration and thus increase the VEGF antagonist dose. EX1003, ¶¶271; *supra*, §VIII.A.

As far back as 2012, Stewart predicted "that increasing the dose of an effective anti-VEGF drug has a greater effect on its durability than its efficacy"—meaning that high concentrations of VEGF antagonist would increase its duration of action in the eye (i.e., trapping VEGF) without reducing its ability to treat angiogenic eye disorders. EX1003, ¶¶84-85, 172; EX1039, 1182. Just two years later, the HARBOR study validated Stewart's prediction, showing that increasing the intravitreal

injection of ranibizumab decreased the number of intravitreal injections a patient had to endure in a year while maintaining efficacy in treating AMD and reported "there were no new safety events observed despite a ***4-fold dose escalation*** in the study." EX1003, ¶¶86, 169; EX1026, 2182. As such, a POSA would have been motivated to similarly increase the dosage of aflibercept by a 4-fold factor (from 2mg to 8mg). EX1026, 2190.

The CLEAR-IT study reported in Nguyen 2012 further suggested "[a]n improvement to the current therapeutic options would be to increase the duration of drug activity, so that intravitreal injections can be administered less frequently" and the study results "help to provide uncontroversial support for a dose-response effect of intravitreal aflibercept in neovascular AMD" noting equal importance in the "lack of any increase in AEs associated with the higher dose, suggesting that the higher dose of intravitreal aflibercept may have increased bioactivity, but did not carry additional risks of deleterious effects during the 8-week study." EX1035, 587; EX1003, ¶167.

A POSA would also have understood that the risk of side effects from a high-concentration aflibercept formulation would be low. As early as 2006, a POSA knew that the "maximum tolerated dose" of aflibercept had not been reached. EX1003, ¶¶167, 179, 271; EX1030, 18. And a POSA knew that doses of 4mg of aflibercept were safe and effective, and, in fact, that "eyes treated with 4 mg intravitreal

aflibercept showed no evidence of inflammation and were indistinguishable from eyes injected with 0.15 mg of intravitreal aflibercept with regard to safety and tolerability." EX1003, ¶¶87; EX1035, 586. A POSA would also know that even a dose of 8mg was "generally well tolerated" and that aflibercept did not show adverse systemic effects even when delivered intravenously in amounts far exceeding that which clinicians deliver to the eye. EX1009, 35; EX1003, ¶¶179, 272-273. This evidence would have motivated the POSA to treat angiogenic eye disorders with high-dose and high-concentration VEGF antagonist formulations without fear of adverse events. EX1003, ¶¶179, 272-273.

A POSA looking to formulate a high-concentration VEGF antagonist—especially aflibercept—would have been aware of, and motivated to look at and combine, the teachings of Regeneron's prior disclosures—Furfine, Dix, and the Label. EX1003, ¶¶ 270-282. Both Furfine and Dix disclose pharmaceutical formulations of VEGF antagonist, including aflibercept, at concentrations up to 100 mg/ml. EX1005, 6:27-32; EX1006, 10:60-11:1, 19:37-42, 20:37-41; EX1003, ¶275. Furfine unequivocally states its pharmaceutical formulations are "suitable for intravitreal administration" (EX1005, 1:16-18) and can be formulated as a "stable liquid ophthalmic formulation" "suitable for ophthalmic use" (*id.*, 6:27-32). And Dix—which issued five years later—both ***discloses and claims*** a pharmaceutical formulation comprising 100 mg/ml VEGF antagonist (aflibercept). EX1006, 10:60-

11:1, 19:37-42 (claim 1), 20:37-41 (claim 2). Dix specifically calls 100 mg/ml "a high concentration" and shows that the 100 mg/ml concentration is in a stable liquid formulation. *Id.*, 2, 20-24. Finally, the Label discloses an 8mg dose of aflibercept was "well tolerated." EX1009, 35. Under these circumstances, a POSA would have been motivated to combine the "interrelated teachings" of Regeneron's prior disclosures. *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1368 (Fed. Cir. 2022).

A POSA would not, however, be limited to Regeneron's teachings regarding aflibercept. Fiedler teaches a plastic pre-filled syringe containing a VEGF antagonist and specifically identifies EYLEA (aflibercept). EX1011, ¶3. Fiedler teaches a POSA that preferable volumes for intravitreal injections to a patient are 30 to 100 µL. *Id.*, ¶29. In fact, the '036 patent incorporates Fiedler by reference. EX1001, 32:61-64. A POSA would have been motivated to combine Fiedler for the same reasons as the Regeneron disclosures—namely they all relate to high-concentration aflibercept formulations. Similarly, Larson teaches target viscosity ranges for high-concentration protein formulations, like those described in Furfine and Dix, that are administered through small-gauge needles. EX1010, ¶¶79, 224, 234. As explained above a POSA would be motivated to combine the teachings of Larson with the Label and the high-concentration formulations taught in Furfine and Dix. *Supra*, §VIII.A.

Thus, as D'Amico explains, the prior art—including the HARBOR and CLEAR-IT clinical studies as well as Regeneron's own disclosures—pointed the POSA toward high-concentration VEGF antagonist formulations for treating angiogenic eye disorders before the earliest priority date of the '036 patent. EX1003, ¶¶271, 165-186; *supra*, §VIII.A.

B. A POSA Would Have Reasonably Expected Success in Treating an Angiogenic Eye Disorder with a High-Concentration VEGF Antagonist Formulation

A POSA would also have had a reasonable expectation of success in treating angiogenic eye disorders with a high-concentration VEGF antagonist of "at least 100 mg/ml" recited in the '036 patent's claims. EX1003, ¶¶270-282.

First, as discussed above, D'Amico explains a POSA would have reasonably expected that high-concentration VEGF antagonist formulations (having a corresponding higher-dosage) would safely and effectively treat the same angiogenic eye diseases as low-concentration VEGF antagonist. *Supra*, §VIII.B.

Moreover, a POSA would have been aware of the HARBOR study, which showed that both doses (0.5mg and 2mg) of ranibizumab (another VEGF antagonist) showed similar results in efficacy and no adverse effects. EX1026, 2187. Thus, as D'Amico explains, a POSA would have had a reasonable expectation that a 4-fold increase in aflibercept dosage would also be safe and effective. EX1026, 2190; EX1009, 35.

Second, to the extent a POSA would have been concerned about the viscosity of high-concentration formulations, Furfine ***already teaches*** that ophthalmic formulations comprising of up to 100 mg/ml VEGF antagonist can be "provided in a pre-filled syringe or vial, ***particularly suitable for intravitreal injection***." EX1005, 2:4:65-67; *see also id.*, 19:31-34 (claim 1 reciting an ophthalmic formulation comprising 1-100 mg/ml of a VEGF antagonist; 0.01-5% of one or more organic co-solvent(s); 30-150 mM tonicity agent; and 5-40 mM of sodium phosphate buffer). And Dix teaches that "high concentration" VEGF antagonist formulations—*e.g.*, 100 mg/ml—can be made into stable liquid formulations. EX1006, 2:20-24; *see also id.*, 10:21-28 (describing stable formulation comprising 100 mg/ml VEGF trap protein, 20 mM histidine, 3% PEG 3350, 1.5% glycine, and 5% sucrose), 10:29-32 (describing Ex. 4 formulation), 10:66-11:1 (describing Ex. 5 formulation).

Larson's teachings, discussed above in Section VIII, provide even more support for desired viscosities of high-concentration protein formulations. Larson teaches that the viscosity of high-concentration biologics must be low enough that the biologic can be administered intravitreally through a 18-32 gauge needle (encompassing the 30-gauge needle taught in the Label). EX1010, ¶¶49; EX1009, 31. Larson teaches that the desired viscosity is "less than about 20 cP, or most preferably less than or about 10 cP…when measured at 25° C." EX1010, ¶¶75, 77. While Larson teaches ***one way*** to reduce viscosity (using organic dyes), a POSA

would have been well aware of ***other ways***—such as the use of a viscosity reducing agent or other excipients "added to the formulation to provide a desired consistency, viscosity, or stabilizing effect." EX1007, ¶96; EX1004, ¶52-70, 127, 198.

For these reasons, a POSA would have had a reasonable expectation of success in achieving the claimed invention. And nothing in the '036 patent claims recite the solution to a viscosity problem. *See* Ground 3, *infra* §X (showing lack of written description for all claims). Either way, the '036 patent's claims are unpatentable.

C. Claim 1

1[A] *A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject*

To the extent the preamble is limiting, Regeneron's prior disclosures teach it. EX1003, ¶¶283-286. Specifically, Furfine teaches ophthalmic formulations of VEGF-specific fusion protein antagonist for pharmaceutical use. EX1005, 1:15-21, 52-59. Furfine teaches VEGF-specific fusion protein antagonists inhibit VEGF. *Id.*, 1:15-27. Furfine also teaches the ophthalmic formulations are "suitable for intravitreal administration to the eye." *Id.*, code [57], 4:65-67. The Label also teaches treating wet AMD, DME, and visual impairment due to macular oedema secondary to CRVO in humans via intravitreal injection of aflibercept into the eye. EX1009, 29-30. As D'Amico explains, all these conditions were well known

angiogenic eye disorders that aflibercept treated. EX1003, ¶¶189-191, 223.

1[B] *in a volume of about 100 microliters or less*

Regeneron's prior disclosures teach, or at the very least, render this limitation obvious in combination with Fiedler. EX1003, ¶¶287-293. Furfine teaches the ophthalmic formulations of VEGF antagonist may be provided in a pre-filled syringe "particularly suitable for intravitreal administration," but does not disclose the volume of the pre-filled syringe. EX1005, 4:65-67; EX1003, ¶289. A volume of about 100 microliters or less, however, was conventional in the art of ophthalmic pharmaceutical formulations, as Fiedler evidenced. EX1003, ¶289.

Fiedler teaches, "[p]referably, a volume of 30 to 100 μL of the liquid formulation is administered to the patient." EX1003, ¶291; EX1004, ¶29. Fiedler's disclosure of 30 to 100 microliters overlaps with the claimed range of about 100 microliters or less, thus rendering the claimed range *prima facie* obvious. *See E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272.

Because Furfine teaches a pre-filled syringe, but does not explicitly disclose the volume, a POSA would have naturally looked to Fiedler for guidance, and combined Fiedler with Regeneron's prior disclosures, because Fiedler also teaches a pre-filled syringe containing a liquid formulation of VEGF antagonist. EX1004, ¶¶18-19; EX1003, ¶291. Indeed, Fiedler teaches a most preferable volume "administered to the patient is 0.05 ml" or 50 microliters. EX1004, ¶67. This

specific disclosure of 50 microliters matches the Label's disclosure of a "50 µL solution for intravitreal injection," as well as the injection volume for other VEGF antagonists delivered to the eye via intravitreal injection (e.g., ranibizumab and bevacizumab)—further evidencing the obviousness of this limitation. EX1009, 29, 32, 34-35; EX1003, ¶292.

Moreover, a POSA seeking to formulate a high-dose pharmaceutical formulation of VEGF receptor fusion protein antagonist (like aflibercept) for intravitreal injection would have had good reason to utilize a volume of about 100 microliters or less as taught by Fiedler, with a reasonable expectation of success. EX1003, ¶293.

The eye is a highly specialized and sensitive organ in the human body, and, as D'Amico explains, intravitreal injection of anti-VEGF therapies can temporarily increase the interocular pressure (IOP) in the eye. EX1003, ¶¶18-22, 70-72, 289. Therefore, physicians who provide intravitreal injections must monitor the patient's IOP post-injection to ensure that there is no sustained increased IOP, which can result in eye damage. EX1003, ¶¶70-72.

Due to the risk of increased IOP with intravitreal injections, POSAs have known for well over a decade that the volume of a VEGF antagonist that may be injected into the eye is limited. EX1003, ¶72. The normal volume of intravitreal injection that does not affect vision, as D'Amico explains, is in the range of 20-100

µL. *Id*. (citing EX1029, 377); *see also* EX1011, ¶29. D'Amico (along with others) reported as part of an expert panel that "injection volumes in excess of 0.1 mL can produce dramatic increases in IOP." *Id*. (citing EX1014, S11). Thus, a POSA would choose a volume of 100 microliters or less, as recited in the claim.

Fundamentally, this limitation merely reflects "routine optimization" of a result-effective variable (volume) and is thus obvious for that reason as well. *Pfizer*, 94 F.4th at 1347.

1[C] *at least 8 mg*

Regeneron's prior disclosures teach, or at the least, render this limitation obvious. EX1003, ¶¶294-297.

The Label discloses an "8 mg" dose. EX1009, 35. While the Label generally provides product information for low-dose EYLEA—i.e., a dose of 2mg aflibercept—it also discloses that some patients received 8mg aflibercept in clinical trials. EX1007, ¶¶26, 32-33. The Label teaches that 8mg aflibercept was "***generally well tolerated***." *Id.*, 35. While the Label termed these 8mg doses "overdoses" (because the intended dose was lower), the Label does not suggest the 8mg dose itself caused any concerns with efficacy or safety. EX1003, ¶295. Indeed, the only concern it identifies is increased interocular pressure from the "increased injection volume" associated with quadrupling the 2mg dose (at 50 microliters) to 8mg (which would be a volume of 200 microliters). *Id*.

Thus, the Label expressly teaches "at least 8 mg." EX1003, ¶295; *see Recor Med., Inc.*, 2025 WL 944511, at *2 ("[A] reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect.") (quotations omitted).

A POSA would have been motivated to treat a patient with a high dose of VEGF antagonist (resulting from a higher concentration), including the "at least 8 mg" recited in the claims, with a reasonable expectation of success. *Supra*, §IX.A-B. As explained above, a POSA would have had good reason to go from low-concentration, low-dose VEGF antagonist formulations to high-concentration, high-dose VEGF antagonist formulations and would have reasonably expected those formulations to treat the same angiogenic eye disorders in a safe and effective manner. *Supra*, §IX.A.

1[D] *of a VEGF receptor fusion protein comprising two polypeptides that comprise an immunoglobulin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component*

Regeneron's prior disclosures teach this limitation because they are all directed to pharmaceutical formulations comprising VEGF antagonist. EX1003, ¶¶298-303. As explained above, the VEGF-specific fusion protein antagonist aflibercept comprises immunoglobulin-like (Ig) domain 2 of a first VEGF receptor (known in the art as "VEGFR1"), Ig domain 3 of a second VEGF receptor (known in the art as "VEGFR2"), and a multimerizing component (the Fc portion of human

IgG antibody). *Supra*, §II.

Furfine's formulation also comprises VEGF trap, which Furfine describes as "consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component." EX1005, 1:52-63. Dix describes VEGF trap identically. *See* EX1006, 1:56-62. The Label also discloses the structure of VEGF trap (aflibercept) and its amino-acid sequence. EX1009, 1-2. As D'Amico testifies, a POSA would recognize these descriptions from the Regeneron's prior disclosures as all describing the same VEGF receptor fusion protein antagonist recited in this limitation. EX1003, ¶¶298-303.

1[E] *wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising at least 100 mg/ml of the VEGF receptor fusion protein*

Regeneron's prior disclosures and Fiedler teach or render this limitation obvious. EX1003, ¶¶304-309; EX1004, ¶¶113, 189-193. Furfine teaches and claims a pharmaceutical formulation of 1-100 mg/ml VEGF-specific fusion protein antagonist. EX1005, 2:4-6, 19:31-34 (claim 1). Dix teaches a "high concentration" formulation comprising 50-100 mg/ml VEGF antagonist. EX1006, 2:12-15. Fiedler teaches VEGF antagonist concentration is between 1 to 100 mg/ml. EX1011, ¶19; EX1004, ¶¶109. These disclosures thus teach formulations with a VEGF antagonist concentration of "at least 100 mg/mL." At a minimum, the disclosed ranges overlap

with the claimed unbounded range of "at least 100 mg/mL," and render this limitation *prima facie* obvious. *E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272.

Dix further ***exemplifies*** and ***claims*** a formulation comprising 100 mg/ml VEGF antagonist. EX1006, 10:60-11:1, 19:37-42, 20:37-41. In Examples 4 and 5, Dix tested the stability of a formulation having 100 mg/ml VEGF trap. *Id.*, 10:1-55, 10:60, 10:65-12:1. Claim 1 of Dix recites a "stable liquid formulation comprising 100 mg/mL of a VEGF antagonist" (*id.*, 19:37-42), and claim 2 recites the "stable liquid formulation of claim 1 consisting of 100 mg/mL of the VEGF antagonist" (*id.*, 20:37-41). Dix thus teaches this limitation.

A POSA would also understand both Furfine's and Dix's "liquid" and "re-constituted" formulations are synonymous with the claimed "aqueous" formulation. Both disclose that their "liquid" formulations are "in water." EX1005, 1:53-55 , 5:45-46; EX1006, 20:37-41 (claim 2 reciting "in water"). Both also contain the identical disclosure that "[l]yophilized formulations are typically reconstituted for use by addition of an ***aqueous*** solution to dissolve the lyophilized formulation" and that a preferred solution is ***water***. EX1005, 7:14-18; EX1006, 5:66-6:3..

1[F] *and having a viscosity of about 5-15 centiPoise (cP) at 20°C*

Regeneron's prior disclosures combined with Larson teaches this limitation. EX1003, ¶¶310-312; EX1004, ¶¶194-199.

Furfine teaches that its formulations are "suitable for intravitreal administration" (EX1005, 1:17-24, 4:65-67) but does not specify a desired viscosity. Fiedler similarly teaches that its formulations are administered intravitreally (EX1011, ¶83), and likewise does not specify a desired viscosity. For the reasons explained in Ground 1, a POSA would have been motivated to look to Larson for desired viscosity values, because Larson, like Regeneron's prior disclosures, also teaches high-concentration liquid formulations that are administered via injection using 30-gauge needles. *Supra*, VIII.A; EX1004, ¶¶195-216.

A POSA would have understood from Larson that a VEGF antagonist formulation (e.g., aflibercept) that is administered intravitreally using a syringe with a 30-gauge needle, as taught in Regeneron's prior disclosures, would have a desired viscosity of about 5-15 cP at 20°C. EX1010, ¶¶75, 77, 224, 234; EX1004, ¶196. Accordingly, a POSA would have had a reasonable expectation of success in obtaining an aqueous pharmaceutical formulation with a protein concentration of at least 100 mg/mL and a viscosity within the claimed range of about 5-15 cP at 20°C. EX1004, ¶¶194-199.

A POSA would also have had a reasonable expectation of success for the reasons discussed above in Ground 1. *Supra*, §VIII.B.; EX1004, ¶¶119-128, 194-199. A POSA was aware of several strategies to improve the viscosity characteristics of high-concentration biologics and would therefore have understood and expected

that any of these available solutions could have been applied to an aqueous pharmaceutical formulation containing at least 100 mg/mL of aflibercept, as taught in Furfine and Dix, if needed to achieve a viscosity of about 5-15 cP at 20°C, as taught in Larson. *Supra*, §VIII.B; EX1004, ¶¶52-70, 198.

Finally, this limitation merely reflects "routine optimization" of a result-effective variable (viscosity) and is obvious for that reason as well. *Pfizer*, 94 F.4th at 1347.

D. Claims 4-34

1. Claims 4-8

Larson teaches the limitations of claims 4-8 for the reasons discussed above in Ground 1. *Supra*, §VIII.D.1; EX1003, ¶¶313-316; EX1004, ¶¶200-214. A POSA would have understood that Larson's teaching of a viscosity of "less than or about 20 cP, or most preferably less than or about 10 cP, when measured at 25° C" (EX1010, ¶¶75, 77) is approximately equivalent to less than or about 22.52 cP, or less than about 11.26 cP at 20°C. EX1004, ¶¶200-214. Because Larson's viscosity ranges encompass the claimed viscosity ranges and values, Larson renders these claims *prima facie* obvious. *E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272; *see also Galderma*, 737 F.3d at 738.

2. Claims 9, 10

Regeneron's prior disclosures teach the limitations of claims 9 and 10.

EX1003, ¶¶317-319; EX1004, ¶¶215-218. Both Furfine and Dix teach that the VEGF antagonist formulations may include a stabilizing agent such as sucrose—a well-known type of sugar. EX1005, 2:15-16; EX1006, 2:3-4; EX1003, ¶318; EX1004, ¶¶216, 218. And, as explained above, the disclosure of sucrose in the prior art teaches the genus "sugar" recited in claim 9 and the alternative sugars recited in claim 10. *Supra*, §VIII.D.2; *see Klein*, 987 F.2d at 1570; *Cuozzo*, 793 F.3d at 1281.

3. Claim 11

Regeneron's prior disclosures teach this limitation. EX1003, ¶¶320-321; EX1004, ¶¶219-220. Specifically, Dix teaches stable formulations comprising a VEGF-specific fusion protein antagonist that include histidine and/or glycine, which are amino acids. EX1006, 10:14-11:1, 19:37-42, 20:37-41; EX1004, ¶220. Thus, the pharmaceutical formulations in Dix "comprise[] an amino acid" as claimed. EX1003, ¶322.

4. Claim 12

Regeneron's prior disclosures teach this limitation. EX1003, ¶322-325; EX1004, ¶221. As D'Amico explains, both the Label and Fiedler teach that VEGF trap is aflibercept. EX1009, 1-2; EX1011, ¶3. Similarly, Furfine and Dix teach the same VEGF trap, which a POSA would have understood is aflibercept. EX1003, ¶325. Indeed, Regeneron described the VEGF trap disclosed in Furfine and Dix as aflibercept to the Patent Office. *See* EX1003, ¶325; EX1013, 2.

5. Claims 13-26

Regeneron's prior disclosures teach the limitations of all these claims. EX1003, ¶¶326-349; EX1004, ¶¶222-235. By the earliest effective filing date of the '036 patent, the use of low-concentration VEGF antagonist (aflibercept) for treating several angiogenic eye disorders was well known. EX1003, ¶¶189-191, 223. For example, as discussed above (*supra*, §VIII.D.5), the Label teaches that aflibercept (**claims 15, 17, 19, 21, 23, 25, 26**) is used to treat neovascular wet AMD (**claim 14**), visual impairment due to macular oedema secondary to CRVO (**claim 24**), DME (**claim 16**), and DR of different severity levels (including proliferative and non-proliferative) (**claims 18, 20, 22**). EX1009, 8-25. It would have been obvious to a POSA that a high-concentration VEGF antagonist (aflibercept) formulation would treat the same angiogenic eye disorders for the reasons discussed above. *Supra*, §VIII.D.5.

Fiedler also teaches a pre-filled syringe containing a liquid formulation of a VEGF antagonist, which is preferably "a soluble VEGF receptor fusion protein" such as aflibercept, for the treatment of several intraocular neovascular (i.e., angiogenic) diseases. EX1011, ¶¶18, 82. A POSA would have been motivated to combine Fiedler with Regeneron's prior disclosures to treat angiogenic eye disorders with a reasonable expectation of success for the reasons discussed above in limitation 1[B]. *Supra*, §IX.C.1[B].

6. Claim 27

As explained above (*supra*, §VIII.D.6.), dependent claim 27 is identical to claim 1 except that it narrows the protein concentration limitation to "about 8 mg aflibercept." EX1001, 62:6-7. Regeneron's prior disclosures teach the limitations of this claim for the same reasons they teach elements 1[C] and 1[D]. EX1003, ¶350; EX1004, ¶236; *supra*, §§IX.C.1[C]-1[D].

Fiedler together with Regeneron's prior disclosures also teaches the limitations of this claim. EX1003, ¶¶350-351. As to "aflibercept," Fiedler teaches that the pre-filled syringe contains a liquid formulation of a VEGF antagonist, which is preferably "a soluble VEGF receptor fusion protein" such as aflibercept. EX1011, ¶18. And, as to "about 8 mg," Fiedler teaches a liquid volume of 30 to 100 μL and a VEGF antagonist protein concentration between 1 to 100 mg/ml for administration to patients. *Id.*, ¶¶19, 29, 67. As D'Amico explains, a POSA would have employed basic mathematics to calculate the amount (in mg) of aflibercept in each of Fiedler's embodiments (*e.g.*, a 100 mg/ml of aflibercept in 80 microliters yields 8mg). EX1003, ¶¶296, 350-351.

7. Claims 28-30

Claim 28, 29, and 30 recite wet AMD (**claim 28**), DME (**claim 29**), and DR (**claim 30**). EX1001, 64:10-13. Regeneron's prior disclosures teach the limitations of all these claims. EX1003, ¶¶352-354; EX1004, ¶¶237-239. A POSA would have

understood that the Label and Fiedler teach that aflibercept treats wet AMD, DME, and DR for at least the reasons discussed above for claims 13, 14, 16, 18, and 27. *Supra*, §IX.D.5. D'Amico explains that a POSA would have understood and recognized that a higher-concentration formulation (i.e., 114.3 mg/ml) of aflibercept would treat the same diseases as the lower-concentration formulation, for the reasons also explained above. *Id.*; *see also supra*, §VIII.D.5.

8. Claim 31

As explained above (*supra*, §VIII.D.8), claim 31: (1) narrows the volume limitation to "about 70 microliters," (2) narrows the dose limitation to "about 8 mg aflibercept," and (3) narrows the protein concentration limitation to "about 114.3 mg/ml." EX1001, 64:16-22; EX1003, ¶¶355-363.

As to "about 8 mg aflibercept," Regeneron's prior disclosures teach this limitation for the reasons explained above in limitations 1[C], 1[D], and claim 27. *Supra*, §§IX.C.1[C]-1[D], IX.D.6; EX1003, ¶¶195-198, 356.

As to "about 70 microliters," Fielder renders this *prima facie* obvious because it falls within Fiedler's disclosed range of "30 to 100 μL." EX1003, ¶291; EX1004, ¶29; *Galderma*, 737 F.3d at 738.

As to "about 114.3 mg/ml," Furfine, Dix, and Fiedler render this limitation obvious. EX1003, ¶252-253, 357; EX1004, ¶¶240-253. As discussed above, Furfine, Dix, and Fiedler each teach stable, high-concentration aqueous

pharmaceutical formulations containing up to 100 mg/mL of aflibercept. *Supra*, §IX.C.1[E]; EX1005, 2:4-9, 2:49-54; EX1006, 10:17-20, 10:60-11:1; EX1011, ¶¶19, 76, cl. 4. Furfine and Fiedler further teach that such formulations are suitable for intravitreal administration. EX1005, 1:17-24, 4:65-67; EX1011, ¶¶52, 83-84.

It would have been obvious for a POSA to increase the concentration from 100 mg/ml to at least 114.3 mg/ml for multiple reasons. First, the difference between 114.3 mg/mL and 100 mg/mL, as taught in Furfine, Dix, and Fiedler, is less than a 15% difference, which, as Falconer explains, is a relatively minor change in protein concentration. EX1004, ¶244. A POSA would ***not*** have expected this increase in concentration (from 100 mg/mL to 114.3 mg/mL) to meaningfully affect the stability and viscosity properties of an aflibercept formulation. EX1004, ¶244. But even if it did, Falconer also explains that it would have been routine for a POSA to make any adjustments necessary to arrive at a stable ophthalmic formulation suitable for intravitreal injection. EX1004, ¶245.

Vitti confirms that a 15% change in protein concentration is relatively minor. EX1004, ¶245. Vitti teaches stable, liquid pharmaceutical formulations containing up to "100±15 mg/mL of a VEGF antagonist" (or 15% greater or less than 100 mg/mL) for intravitreal administration via a syringe fitted with a 30-gauge needle. EX1007, ¶¶94, 108, 115, 127. That teaching (i.e., that 85 to 115 mg/ml aflibercept is suitable for intravitreal injection) confirms or at least suggests that a formulation

having the claimed concentration (i.e., 114.3 mg/mL) would likewise be stable and suitable for intravitreal administration through a 30-guage needle. EX1004, ¶245. Accordingly, given the relatively minor increase in concentration from the 100 mg/mL aflibercept formulations taught in Furfine, Dix, and Fiedler to the claimed 114.3 mg/ml concentration, a POSA would have reasonably expected success in obtaining an aqueous pharmaceutical formulation with 114.3 mg/mL aflibercept. EX1004, ¶247.

Second, as explained in detail above, skilled artisans' desire to ameliorate the treatment burden associated with long-term, frequent intravitreal injections drove a movement in the field of anti-VEGF drugs toward higher-dose, higher-concentration formulations. EX1003, ¶¶71-72, 359-360; *supra*, §IX.A. Accordingly, a POSA would have been motivated to increase the concentration of the 100 mg/mL aflibercept formulations taught in Furfine, Dix, and Fiedler to achieve that objective. EX1003, ¶¶71-72, 359-360.

To do so, a POSA would have naturally started with a dose of at least about 8mg, because the Label teaches that dose was "generally well tolerated." EX1009, 35; *see also supra*, §IX.C.1[C]; EX1003, ¶¶295.

Next, the POSA would consider the injection volume. As noted above, the injection volume for commercially-available VEGF antagonist formulations ranged from 50 μL to 90 μL, and a POSA knew that 100 μL was the upper safe volume

limit. *Supra*, §VIII.C.1[B]. As D'Amico explains, while any injection volume between 50 µL and 100 µL would have been clinically acceptable, a POSA would have been motivated to use a lower injection volume to lower the risk of adverse clinical events. EX1003, ¶¶71-72, 359.

The Label teaches low-concentration EYLEA was delivered in a 50 µL volume (EX1009, 29-30, 32, 34-35), as were other VEGF antagonists on the market at the time (Lucentis® and Avastin®). EX1003, ¶71-72, 359. D'Amico explains that a clinician would have preferred to deliver the 8mg dose in the same 50 µL volume or a volume as close to 50 µL as possible, which would necessarily require a higher concentration of aflibercept. *Id.*

Given these parameters, a skilled formulator would have determined the range of possible concentrations for aflibercept in the aqueous pharmaceutical formulation is 80 mg/mL to 160 mg/mL as set forth below:

Dose (mg)	Injection Volume (µL)	Concentration (mg/mL)
8	50	160
8	60	133.3
8	**70**	**114.3**
8	80	100
8	90	88.9
8	100	80

EX1004, ¶¶248-250. And as shown above, a skilled formulator would have been motivated to create a stable aqueous pharmaceutical formulation for intravitreal administration containing 114.3 mg/mL aflibercept, and would have reasonable

expectation of success in doing so, as a matter of routine optimization based on the teachings of Furfine, Dix, and Fiedler. EX1004, ¶250; *Pfizer, Inc. v. Apotex*, 480 F.3d at 1368; *Pfizer*, 94 F.4th at 1347; *Valeant,* 955 F.3d at 34.

On the other end, a POSA would not have been motivated to go above 115 mg/ml, the upper limit disclosed in Vitti. EX1007, ¶¶87, 94. While a skilled formulator may have been able to obtain an aflibercept formulation having a protein concentration above 115 mg/mL, that POSA would have understood that higher concentrations increased the risk of product failure, from, e.g., increased aggregation and viscosity. EX1004, ¶251.

Overall, a POSA team would have recognized that the clinical considerations related to patient treatment burden and adverse clinical events described by D'Amico (which favor a higher protein concentration to deliver an 8mg dose of aflibercept at a lower-volume) (EX1003, ¶363) had to have been balanced with the competing formulation considerations related to aggregation and viscosity described by Falconer (which favor a lower protein concentration to deliver the same 8mg dose at a higher volume) (EX1004, ¶252). A skilled formulator working with a skilled clinician would have recognized that a formulation containing 114.3 mg/mL of aflibercept (for providing an 8mg dose at a volume of 70 µL) would have been a suitable option. EX1004, ¶252. A skilled formulator would have reasonably expected to successfully obtain a formulation suitable for intravitreal injection at

114.3 mg/ml based on Furfine, Dix, and Fiedler as a matter of routine optimization. EX1004, ¶253. A skilled clinician would find the 70 μL volume—slightly more than 50 μL of prior treatments but less than 100 μL—to be a reasonable volume to improve the patient experience and minimize potential adverse events. EX1003, ¶363.

9. Claims 32-34

Fiedler together with Regeneron's prior disclosures teaches the limitations of these claims for the same reasons they teach claims 14, 16, 18, and 31, discussed above. *Supra*, §§IX.D.5., IX.D.8; EX1004, ¶¶254-256; EX1003, ¶¶364-365. As D'Amico explains, a POSA would have understood and recognized that a higher-concentration formulation (i.e., 114.3 mg/ml) of aflibercept would treat the same diseases as the lower-concentration formulation, for the reasons also explained above. *Supra*, §VIII.D.5; EX1003, ¶171.

E. Claim 35

35[A] *A method for treating an angiogenic eye disorder in a human subject in need thereof comprising administering, intravitreally into the eye of the subject*

To the extent the preamble is limiting, Regeneron's prior disclosures teach it for the same reasons that they teach limitation 1[A], as explained above. *Supra*, §IX.C.1[A]; EX1003, ¶366.

35[B] *about 70 microliters or less*

Regeneron's prior disclosures and Fiedler in view of Larson render this limitation obvious for the reasons discussed above in claim 31. *Supra*, §IX.D.8; EX1003, ¶367.

35[C] *of an aqueous pharmaceutical formulation comprising about 103-126 mg/ml of aflibercept*

Regeneron's prior disclosures and Fiedler render this limitation obvious for the reasons discussed above in claim 31. *Supra*, §IX.D.8; EX1003, ¶¶368-369; EX1004, ¶¶240-253, 257. As explained above, based on an aflibercept dose of 8mg and an injection volume of 50 μL to 100 μL, a skilled formulator would have been able to identify a range of concentrations, and would have reasonably expected to succeed in obtaining a stable aqueous pharmaceutical formulation for intravitreal administration containing up to about 115 mg/mL aflibercept as a matter of routine optimization. *Supra*, §IX.D.8.; EX1004, ¶¶257-260. And because this protein concentration range (up to about 115 mg/ml) overlaps with the claimed range (103-126 mg/ml), the limitation is *prima facie* obvious. *E.I. DuPont*, 904 F.3d at 1008; *Almirall,* 28 F.4th at 272.

35[D] *and having a viscosity of about 5-15 cP at 20^{o}C*

Regeneron's prior disclosures in view of Larson render this limitation obvious for the reasons discussed above in limitation 1[F] and claim 31. *Supra*, §§IX.C.1[F], IX.D.8.; EX1003, ¶370; EX1004, ¶¶194-199, 240-253, 257. In particular, as Falconer explains, a POSA would have understood that Larson teaches aqueous

pharmaceutical protein formulations that have a viscosity of about 5-15 cP at 20°C. *Supra*, §IX.C.1[F] (EX1004, ¶196). A POSA would have had a reasonable expectation of success of obtaining a viscosity of about 5-15 cP at 20°C for the reasons discussed above in limitation 1[F] and claim 31. *Supra*, §§IX.C.1[F], IX.D.8.; EX1004, ¶¶194-199, 240-253.

F. Claims 36-38

Regeneron's prior disclosures together with Fiedler teaches the limitations of these claims for the same reasons they teach claims 13, 14, 16, 18, 28-30, and 32-34, discussed above. *Supra*, §§IX.D.5., IX.D.8; EX1004, ¶¶261-263; EX1003, ¶¶371-372. As D'Amico explains, a POSA would have understood and recognized that a higher-concentration formulation of aflibercept (i.e., 103-126 mg/ml) would treat the same diseases as the lower-concentration formulation, for the reasons explained above. *Supra*, §VIII.D.5.

X. GROUND 3: CLAIMS 1-38 ARE UNPATENTABLE FOR LACK OF WRITTEN DESCRIPTION

Regeneron's claims also suffer from another problem—the specification does not show the inventors possessed formulations reflecting the full scope of the claims that would achieve the required viscosity levels, rendering all challenged claims unpatentable for lack of written description under 35 U.S.C. §112(a). EX1004, ¶¶264-286.

The test for written description is "whether the disclosure of the application

relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). This requirement is satisfied when the specification "set[s] forth enough detail to allow a POSA to understand what is claimed and to recognize that the inventor invented what is claimed." *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 928 (Fed. Cir. 2004). Thus, the specification "must lead a person of ordinary skill in the art to understand that the inventor possessed ***the entire scope*** of the claimed invention," not just a few embodiments. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1337 (Fed. Cir. 2021).

As discussed below, the disclosure of formulations that meet the claimed viscosity limitations reflect only a small corner of the claimed genus, and all disclosed formulations contain a buffer, a component not required by the claims. Based on these disclosures, a POSA would not understand the inventors to have possessed anything close to the full scope of the potential claimed formulations that would achieve the claimed viscosity levels. Indeed, Regeneron's own specification teaches no more about making high-concentration formulations with the claimed viscosity levels than the prior art and, under the law, Regeneron must do ***more*** than enough to render the claims obvious. *See Ariad*, 598 F.3d at 1352 ("[A] description that merely renders the invention obvious does not satisfy the [written description]

requirement."). Thus, the challenged '036 claims lack written description support.

A. The Challenged Claims Lack Written Description Because the Specification Fails to Show Possession of Their Full Scope

1. The Challenged Claims Recite a Broad Genus of Pharmaceutical Formulations with Functional Requirements but Narrow Examples

The challenged claims cover a method for treating an angiogenic eye disorder comprising intravitreal administration of a massive genus of potential formulations, while failing to specify any components of the formulation other than the VEGF fusion protein itself, including whether it contains a buffer, a surfactant, a viscosity-reducing agent, or a thermal stabilizer, all components that are discussed in the specification, let alone the identity or concentration of any such component. Even the narrowest claims add only the requirement that the formulation contains a sugar, or an amino acid.

The viscosity limitation, most broadly recited as 5-15 cP at 20°C, is a functional feature—it recites a desired result of the claimed formulation. These types of functional limitations raise more written description issues than claims without such limitations. *Ariad*, 598 F.3d at 1349 ("The [written description] problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus.").

In contrast to the broad genus of formulations potentially covered by the claims, the specification discloses only a small number of species that achieve the

required viscosity, and all those species contain a buffer. The case law makes clear this disclosure of a small number of species in a small corner of the massive claimed genus cannot support the '036 patent's broad claims that cover any 100 mg/mL or greater VEGF formulation that meets the viscosity limitation. *See AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

The specification only provides viscosity data for a subset of those VEGF antagonist formulations, all of which are similar in formulation components. EX1001, Figs. 3A-C, 5, 9; EX1004, ¶269. Viscosity data is shown in Figures 3A-3C and Figures 5 and 9. EX1001, Figs. 3A-C, 5, 9. The formulations of Figures 3A and 3B contain 155 mg/ml VEGF Trap in either 10 mM sodium phosphate or histidine buffer, and 5% sucrose, in combination with no inorganic salt, arginine, lysine, sodium chloride and magnesium chloride. EX1001, 38:37-54, Figs. 3A-B; EX1004, ¶270. The formulations tested in Figure 3C have 10 mg/mL to 160 mg/mL VEGF Trap, 10 mM sodium phosphate buffer, and 5% sucrose, some with arginine and some without. EX1001, 38:55-67, Fig.3C; EX1004, ¶270. The Figure 5 formulations have the same VEGF concentration range and either phosphate or histidine buffer. EX1001, Fig.5; EX1004, ¶271. All formulations tested in Table A (Fig. 9) contain a histidine buffer, as well as sucrose and polysorbate 20. EX1001, Table A; EX1004, ¶272; EX1003, 101.

Falconer explains that, although the tested formulations represent only a small fraction of the claimed formulations, the viscosity data demonstrates that the specific formulation components and percentages matter to achieving the required viscosity levels. EX1004, ¶273. For example, all the tested formulations that contain a histidine buffer fall within the claimed viscosity range of 5-15 cP. *See* Ex. 1001, Table 3-2. The tested formulations containing a phosphate buffer, however, sometimes fall above the claimed range, showing viscosities of up to 17.3 cP. See EX1001, Table 3-1. As the specification explains, "[a]t higher VEGF Trap concentrations, the histidine buffer showed an improvement in viscosity (relative to phosphate)." EX1001, 42:19-21. Thus, the only formulations even tested have a buffer, and the specification demonstrates even the ***type*** of buffer impacts the formulation's viscosity and whether it falls within the claimed range or not. EX1004, ¶273.

Moreover, the claims recite concentrations of at least 100 mg/mL of VEGF fusion protein, with no stated upper limit. But Figure 5 demonstrates that, above about 160 mg/mL, the viscosity of both phosphate and histidine-containing formulations falls ***well above*** the claimed range. *See* EX1001, Fig.5; EX1004, ¶274. There are ***no examples*** of VEGF fusion protein concentrations above 155 mg/mL that achieve the required viscosity levels. EX1004, ¶275.

2. The Limited Examples Provided Fail to Show Possession of the Claimed Genus

The narrow disclosures in the specification do not demonstrate the inventors had possession of anything close to the full scope of the claimed genus—all the VEGF fusion protein formulations with a concentration of at least 100 mg/mL (that can deliver 8mg of the VEGF fusion protein in 100 microliters or less) with a viscosity of 5-15 cP.

Written description requires structural features "of species falling within the genus ***sufficient to distinguish the genus from other materials***." *Ariad*, 598 F.3d at 1350. Here, because the specification lists only a few examples, it does not provide the required information "sufficient to distinguish the genus from other materials." *Ariad*, 598 F.3d at 1350; *AbbVie*, 759 F.3d at 1300 (explaining that if "the disclosed species only abide in a corner of the genus" the claims lack written description support). EX1004, ¶276. As Falconer explains, the disclosure in the specification fails to provide a POSA with sufficient information about which potential options for formulations will achieve the required viscosity levels and which will not; EX1004, ¶276. Likewise, there is no disclosure of a representative number of species in the genus because, as discussed above, the disclosed species are highly similar to one another, including all having a buffer when the claim allows for no buffer, and do not reflect the full scope of the claims. EX1004, ¶276.

The facts are similar to *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d, 566 (D. Del. 2018), *aff'd*, 945 F.3d 1184 (Fed. Cir. 2019). The *Pernix* inventors conducted a clinical study on an extended-release (ER) hydrocodone product and found patients with hepatic impairment would not need a dose adjustment relative to non-impaired patients, as evidenced by certain pharmacokinetic results. 323 F. Supp. 3d at 573-74. The inventors then obtained patent claims covering *any* ER formulation that achieved those functional results in patients regardless of hepatic impairment, and not limited to the formulation that was shown to achieve those results. *Id*. at 575.

Citing *Ariad*, the district court explained that "[t]he issue is whether the species that were disclosed in the specification are sufficient to justify a conclusion that the inventor of the species actually invented—and is entitled to claim—the genus that is recited in the claims." *Id*. at 619-20. This is the same problem with the '036 claims. The specification shows only that a narrow group of formulations achieve the claimed results, yet the claims recite effectively any high-concentration VEGF fusion protein formulation, regardless of components, that achieves those results. EX1004, ¶276.

3. The Examiner Initially Recognized the Written Description Problem but Erroneously Believed Regeneron Overcame It

During prosecution, the examiner rejected pending claims, which at the time

broadly recited methods of treating angiogenic eye disorders through intravitreal injection of 8mg of a VEGF receptor fusion protein. EX1002, 2140-2148. The Examiner explained, "while the specification provides adequate written description for stable, high-concentration formulations of a VEGF receptor fusion protein along with 5% sucrose, polysorbate, a histidine based buffer, and L-arginine, it does not provide adequate written description for the breadth of the formulation encompassed by the claims." *Id.*, 2145.

In response, the Applicant amended the claims to add the limitations related to volume (100 μL or less), protein concentration (greater than 100 mg/mL, and viscosity (5-15 cP). EX1002, 758. With that amendment, the Examiner withdrew the rejection and allowed the claims. EX1002, 2140-2148. This was erroneous.

The Examiner erred in finding that the amended claims (i.e., the challenged claims) have support. These amended claims do not address the written description problem of failing to specify the elements of the composition that allow for the high-dose and, indeed, inject the new problem of failing to specify the elements of the composition that would achieve the recited viscosity levels. The high-concentration limitation that was added to the claims certainly cannot help in this regard. Indeed, the specification explains "high concentration antibody and protein formulations often contend with ***increased protein aggregation and viscosity***, which results in lower overall antibody or protein potency, and lower manufacturing and poorer

storage stability." EX1001, 1:61-65. As Falconer explains, a POSA would have understood that the high-concentration was part of the ***problem*** for viscosity, not part of the solution. EX1004, ¶50. The other unclaimed formulation components are critical to achieving the required viscosity, as the data in the specification demonstrates and Falconer confirms. EX1004, ¶273.

B. The Challenged Claims Lack Written Description Support Because They Do Not Recite a Buffer

The challenged claims also lack written description support because they do not require a buffer, which the specification makes clear is required. EX1004, ¶¶277-286. Every example in the specification contains a buffer, never suggesting it is optional. EX1001, 2:34-50, 7:61-66, 14:65-5:3, 20:2-6, 23:22-28:20, EX1004, ¶¶278-284. And the specification shows that the buffer has an impact on the viscosity. EX1004, ¶273. Because the specification fails to demonstrate possession of a formulation that achieves the claimed viscosity levels without a buffer, the claims lack written description support.

All formulations for which the '036 patent includes viscosity data contain a buffer. Similarly, all 89 specified "[i]llustrative formulations" also include buffers. EX1001, 23:22-28:20; EX1004, ¶279. The description of many of these illustrative formulations expressly states when a particular component is not required. *Id.* For example, the description of Formulation G states that the formulation "specifically

exclude[es] a viscosity reducing agent." EX1001, 23:44-47; EX1004, ¶279; *see also id.*, 23:48-66 (Formulations H-L), 24:20-43 (Formulations S-X), 24:62-25:19 (Formulations EE-JJ), 25:38-61 (Formulations QQ-VV).

Throughout the specification, the buffer, as opposed to other components, is ***always*** included in the disclosed formulations. *See, e.g.*, EX1001, 2:34-40 ("Embodiments herein provide formulations having a VEGF receptor fusion protein, ***a buffer***, a thermal stabilizer, a viscosity reducing agent, and a surfactant. In other embodiments, the formulations do not include a viscosity reducing agent."); *see also id.*, 14:65-15:3.

Where the specification wants to treat a component as optional, it does so. For example, it expressly states that viscosity reducing agents and thermal stabilizers are optional. EX1001, 2:41-50 ("In an embodiment of the invention, a pharmaceutical formulation of the present invention is provided having…***optionally*** a thermal stabilizer and/or a viscosity reducing agent…."); s*ee also id.*, 2:36-38; *id.*, 20:2-6; *see also id.*, 14:65-15:3; *id.*, 2:41-50; *see also id.*, 5:11-18. The buffer, however, is ***never*** characterized as optional. EX1004, ¶¶281-284.; EX1001, 7:61-66.

In light of *every* formulation (more than 83 embodiments) in the specification having a buffer, the statements in the specification demonstrating that the buffer is not an optional ingredient, and the data in the specification showing that the presence of a buffer impacts the viscosity of the formulation, the '036 patent claims also lack

written description because the claims do not recite a key limitation present in the compositions that are shown by the specification to meet the claimed viscosity limitations—a buffer. EX1004, ¶185.

The facts are like those that led to summary judgment of invalidity for lack of written description in *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336 (Fed. Cir. 2005). There, the specification disclosed a method for creating a seamless discrete wavelet transform (DWT) by dividing an image into smaller tiles for calculation purposes and then applying DWT to each tile individually. *Id.* at 1339. "[T]he specification "provide[d] only one method for creating a seamless DWT, which is to 'maintain updated sums' of DWT coefficients." *Id.* at 1344; *see also id.* at 1340. Claim 21, though, broadly covered *any* method of creating a seamless DWT, including methods that did not perform the step of "maintaining updated sums," which was the only method disclosed in the specification. *Id.* at 1343. The Federal Circuit explained that a POSA "would not understand LizardTech to have invented a method for making a seamless DWT, except by 'maintaining updat[ed] sums of DWT coefficients.'" *Id.* at 1345; *see also Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998).

So too here. The specification demonstrates to a POSA the inventors did not invent, or even contemplate, high-concentration VEGF formulations with the specified viscosity levels that do not contain a buffer. Every disclosed formulation

that meets the claimed viscosity levels contains a buffer; in fact, every disclosed formulation, even those for which viscosity was not tested contains a buffer. EX1004, ¶286. And the specification never suggests that a buffer could be optional. EX1004, ¶286. Because the specification supports only formulations with a buffer that achieve the claimed viscosity levels, yet the claims broadly cover any high-concentration VEGF formulation that would meet those levels, the claims are invalid for lack of written description. EX1004, ¶286.

XI. GROUND 4: CLAIMS 2 AND 3 ARE UNPATENTABLE FOR OBVIOUSNESS OVER LARSON, VITTI, AU EYLEA LABEL, AND 2011 EYLEA CLINICAL REVIEW

Claims 2 and 3 would have been obvious over the Ground 1 references in combination with the Clinical Review. EX1003, ¶¶373-383; EX1004, ¶¶287-288. A POSA would have been motivated to combine the Ground 1 references, with a reasonable expectation of success, for the reasons described above in Ground 1. *Supra*, §VII.A-B.

Claim 2 recites that the subject "maintains or achieves a reduction in central retinal thickness" whereas claim 3 recites that the subject "maintains and achieves an improvement in best corrected visual acuity." EX1001, 61:62-62:2.

The Label teaches that patients maintained or achieved a reduction in central retinal thickness following intravitreal injection of aflibercept. EX1009, 3, 6 (stating that for DME "[r]apid and robust response in morphology (central retinal thickness

[CRT]) as assessed by OCT was seen soon after treatment initiation"); EX1003, ¶¶375-378. The Label also teaches that patients maintained visual acuity under the Best Corrected Visual Acuity (BCVA) test. EX1009, 8-10; EX1003, ¶¶375-378.

Claims 2 and 3 also recite that the subject "does not experience a significant increase in blood pressure." EX1001, 61:62-62:2. As D'Amico explains, a POSA would have already known that aflibercept did not cause a significant increase in blood pressure based on the Clinical Review. EX1003, ¶¶379-382.

The Clinical Review is another Regeneron disclosure providing a summary of the pharmacological and biopharmaceutical findings from several EYLEA clinical trials. EX1008, 1-3. A POSA concerned with aflibercept, would have been naturally motivated to look at all clinical trials involving aflibercept, including the Clinical Review. EX1003, ¶379. Upon doing so, the POSA would have learned that following intravitreal administration, "aflibercept was not observed to cause increases in DBP [diastolic blood pressure] or SBP [systolic blood pressure]." EX1008, 10-11 (citing Fig.2.2.4.2-1). Accordingly, a POSA would have recognized and understood well before the '036 patent that—based on the Ground 1 references in combination with the Clinical Review—that intravitreal injection of aflibercept does not "cause a significant increase in blood pressure" as claimed.

Moreover, as D'Amico explains, a POSA would have reasonably expected that intravitreal injection of higher-concentration aflibercept (i.e., at least 100

mg/ml) would have the same clinical effects (i.e., maintenance or achievement of "reduced central retinal thickness" and "improvement in best corrected visual acuity" and no "significant increase in blood pressure"). *Supra*, §VIII.D.5; EX1003, ¶382. Indeed, the Label teaches that intravitreal injection of 8mg aflibercept was "generally well tolerated" and says nothing about a "significant" increase in blood pressure. EX1009, 35; EX1003, ¶¶382-383.

XII. GROUND 5: CLAIMS 2 AND 3 ARE UNPATENTABLE FOR OBVIOUSNESS OVER FURFINE, DIX, FIEDLER, AU EYLEA LABEL IN VIEW OF LARSON AND 2011 EYLEA CLINICAL REVIEW

Claims 2 and 3 also would have been obvious over the Ground 2 references further in view of the Clinical Review. EX1003, ¶¶384-390; EX1004, ¶¶289-290.

A POSA would have been motivated to combine the Ground 2 references, with a reasonable expectation of success, for the reasons described above in Ground 2. *Supra*, §IX.A-B.

As to the limitations in claims 2 and 3 directed to central retinal thickness best corrected visual acuity, the Label renders these limitations obvious for the reasons discussed above in Ground 4. *Supra*, §XI; EX1003, ¶¶373-383, 386-387.

As to the "blood pressure" limitation, the Clinical Review together with the Ground 2 references renders this limitation obvious for the reasons discussed above. *Supra*, §XI; EX1008, 1-3; EX1003, ¶¶379-382. The Clinical Review teaches that

intravitreal administration of aflibercept did not cause increases in blood pressure. EX1008, 10-11 (citing Fig.2.2.4.2-1); EX1003, ¶¶379, 388. As explained above with Ground 1, POSA would have been naturally motivated to combine the Clinical Review with the Ground 2 references and expected that intravitreal injection of higher-concentration aflibercept (i.e., at least 100 mg/ml) would have the same clinical effects for the reasons discussed above. *Supra*, §XI; EX1003, ¶¶384-390.

XIII. PAYMENT OF FEES – 37 C.F.R. § 42.203

Petitioner authorizes the Patent and Trademark Office to charge any fees to Deposit Account No. 501814.

XIV. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(A)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

The real party-in-interest for Petitioner is Biocon Biologics Limited. In addition, in order to assist members of the Board in identifying potential conflicts, Trial Practice Guide, 77 Fed. Reg. 48,756, 48,759 (20212), Biocon also identifies the following additional parties pursuant to § 42.8(b)(1): Biocon Limited, Biocon Biologics Inc., and Biocon Biologics Ireland Limited.

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

Post-grant review has been instituted for the ’036 patent in PGR2025-00085. Petitioner is not aware of any disclaimers, reexamination certificates, or other petitions for inter *partes* or post-grant review for the ’036 Patent, nor is Petitioner

aware of any pending civil actions involving the '036 patent. Pending U.S. Application Nos. 18/367,444 and 18/984,981 claim priority to the '036 patent.

C. Lead And Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner provides the following designation of counsel.

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XV. CONCLUSION

For the above reasons, claims 1-38 are unpatentable. Petitioner respectfully requests that the Board grant the Petition and cancel claims 1-38 for unpatentability.

Respectfully submitted,

Dated: April 02, 2026

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CERTIFICATE OF COMPLIANCE

I hereby certify that the word count for the foregoing Petition for Post Grant Review complies with the type-volume limitations of 37 CFR § 42.24(d) because it contains fewer than the 18,700 words (as determined by the Microsoft Word word processing system used to prepare the brief), excluding the parts of the brief exempted by 37 CFR § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e)(4)(i) *et seq.* and 42.105(b), I hereby certify on this second day of April, 2026, a complete and entire copy of this Petition for Post Grant Review and all supporting exhibits were provided by Federal Express, to the Patent Owner, by serving the correspondence address of record as follows:

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