IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

REGENERON PHARMACEUTICALS, INC.,

Plaintiff,

v. **CIVIL NO. 1:22-CV-61 (KLEEH)**

MYLAN PHARMACEUTICALS INC., and BIOCON BIOLOGICS, INC.,

Defendants.

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MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

I. INTRODUCTION

In this patent infringement action, the plaintiff, Regeneron Pharmaceuticals, Inc., ("Regeneron"), and the Defendants, Mylan Pharmaceuticals Inc. and Biocon Biologics, Inc. (collectively, "the Defendants"),[1] dispute whether the Defendants have infringed claims 6 and 25 of Regeneron's U.S. Patent No. 11,253,572 ("the '572 Patent"); Claims 11 and 19 of Regeneron's U.S. Patent No. 10,888,601 ("the '601 Patent"); and claims 4, 7, 9, 11, 14, 15, 16, and 17 of Regeneron's U.S. Patent No. 11,084,865 ("the '865 Patent"). They also dispute whether each of these asserted claims is valid and enforceable.

[1] Regeneron initially brought this lawsuit against only Defendant Mylan Pharmaceuticals Inc. ("Mylan"). (ECF No. 1). Defendant Biocon Biologics, Inc. was added later by stipulation (ECF No. 523).

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Regeneron has sued the Defendants under the Biologics Price Competition and Innovation Act ("BPCIA"), which "governs a type of drug called a biosimilar, which is a biologic product that is highly similar to a biologic product that has already been approved by the Food and Drug Administration (FDA)." Sandoz Inc. v. Amgen Inc., 582 U.S. 1, 5 (2017). The BPCIA provides an abbreviated route for FDA approval of biosimilars.

The patents-in-suit are associated with Regeneron's FDA approved Eylea® product, which contains a biological product known as aflibercept. The Defendants filed a Biologics License Application ("BLA") seeking FDA approval to market a biosimilar aflibercept product under the trade name Yesafili™ prior to the expiration of the patents in suit.[2] The Court is tasked with deciding the following:

(1) whether the Defendants' BLA products infringe claims 4, 7, 9, 11, 14, 15, 16, and 17 of the '865 Patent;

(2) whether the Defendants' proposed label induces infringement of claims 6 and 25 of the '572 Patent and claims 11 and 19 of the '601 Patent;

[2] Mylan filed BLA No. 761274 with the FDA on October 29, 2021. It transferred ownership of that BLA to Biocon effective March 31, 2023. (ECF No. 523).

(3) whether claims 4, 7, 9, 11, 14, 15, 16, and 17 of the '865 Patent are invalid as anticipated or obvious or invalid under 35 U.S.C. § 112 for lack of written description, lack of enablement, or indefiniteness;

(4) whether claims 6 and 25 of the '572 Patent are invalid as anticipated or obvious or invalid under 35 U.S.C. § 112 for lack of written description, lack of enablement, or indefiniteness; and

(5) whether claims 11 and 19 of the '601 Patent are invalid as anticipated or obvious or invalid under 35 U.S.C. § 112 for lack of written description, lack of enablement, or indefiniteness.

Following a nine-day bench trial, the parties submitted their memoranda of law of these issues, and the case is ripe for the Court's decision.

II. FINDINGS OF FACT

A. Parties, Jurisdiction, and Venue

Regeneron is a corporation organized under the laws of the State of New York, with its principal place of business at 777 Old Saw Mill River Road, Tarrytown, NY 10591. Mylan is a company organized under the laws of the State of West Virginia with its principal place of business at 3711 Collins Ferry Road, Morgantown, West Virginia 26505. Mylan is an indirect wholly-owned subsidiary

of Viatris Inc. Biocon is a company based in India. The Court has subject matter and personal jurisdiction, and venue in this District is proper.

B. The BPCIA

Under the Public Health Service Act ("PHSA"), a sponsor seeking to market a biologic drug must file a BLA with the Food and Drug Administration ("FDA") that details the biologic's chemistry, pharmacology, manufacturing process, and medical effects. Sandoz, 582 U.S. at 6. Through the BPCIA, Congress amended the Public Health Service Act and the Patent Act in an effort to balance the goals of competition and innovation. BPCIA § 7001(b), Pub. L. No. 111-148. To expedite getting competing "biosimilars" to market, Congress created an abbreviated regulatory approval pathway so that the biosimilar applicant does not have to regenerate early preclinical and clinical studies; rather, the applicant can instead rely, in part, on the data supporting the previous approval of a reference biologic product. 42 U.S.C. § 262(i)(2), (k); Sandoz, 582 U.S. at 7. A biosimilar "is a biologic product that is highly similar to a biologic product that has already been approved." Sandoz, 582 U.S. at 5.

The Defendants' BLA for its biosimilar product, Yesafili, relies on the Eylea BLA data as the reference biologic product

under the statute. (ECF No. 1, ¶ 3; ECF No. 435, Answer to ¶ 3). To compensate the reference product sponsor ("RPS"), here Regeneron, for the use of these data, Congress grants the RPS a valuable twelve (12) years of marketing exclusivity, independent of any patent protection to which it is entitled. Sandoz, 582 U.S. at 7 ("the manufacturer of a new biologic enjoys a 12-year period when its biologic may be marketed without competition from biosimilars"). Regeneron's marketing exclusivity period (which includes an additional extension for performing a pediatric study) is set to expire on May 18, 2024. ECF Nos. 5, 7.

C. Procedural Background

By letter dated January 5, 2022, Mylan notified Regeneron that "FDA has received a BLA from Mylan for M710, a proposed biosimilar to aflibercept, which was submitted under 42 U.S.C. § 62(k)." By letter dated February 22, 2022, Regeneron served on Mylan a list of patents pursuant to 42 U.S.C. § 262(l)(3)(A), that Regeneron believed "could reasonably be asserted against a person 'engaged in the making, using, offering to sell, selling or importing into the United States of the biological product that is the subject of' Mylan's BLA No. 761274." Regeneron's list of patents pursuant to 42 U.S.C. § 262(l)(3)(A) included each patent-in-suit as well as additional patents. Mylan subsequently served

detailed statements related to the identified patents, on April 14, 2022, pursuant to 42 U.S.C. § 262(l)(3)(B). Regeneron provided its responsive detailed statements on June 10, 2022, pursuant to 42 U.S.C. § 262(l)(3)(C). The parties conducted negotiations pursuant to 42 U.S.C. § 262(l)(4)(A) and exchanged lists of patents to litigate pursuant to 42 U.S.C. § 262(l)(5)(B).

Pursuant to 42 U.S.C. § 262(l)(6)(B), Regeneron brought suit against Mylan on the patent-in-suit, among other patents, on August 2, 2022.[3] In accordance with the Court's Scheduling Order, following claim construction, Regeneron reduced its asserted patents and claims to claims 11, 19, and 27 of the '601 Patent, claims 4, 7, 9, 11, and 14-18 of the '865 Patent and claims 6, 7, 12, 13, 18, 19, 22, 23, and 25 of the '572 Patent. (ECF No. 433). Regeneron also stipulated to the invalidity of claims 5-6 and 9 of the '601 Patent and claims 1-5, 8-11, 14, 26-28 of the '865 Patent under the Court's claim construction. Id.

Thereafter, the parties filed cross motions for summary judgment, which the Court denied. (ECF Nos. 428, 429, 525). The Court held a final pretrial conference on May 30, 2023. (ECF No.

[3] Regeneron sued on 24 patents, U.S. Patent Nos. 7,070,959; 9,222,106; 9,254,338; 9,669,069; 9,816,110; 10,130,681; 10,406,226; 10,415,055; 10,464,992; 10,669,594; 10,857,205; 10,888,601; 10,927,342; 10,973,879; 11,053,280; 11,066,458; 11,084,865; 11,104,715; 11,174,283; 11,186,625; 11,253,572; 11,299,532; 11,306,135; and 11,332,771. (ECF No. 1, ¶ 6).

512). The Court denied the Defendants' request to challenge inventorship, and to challenge the enforceability of the claims based on inequitable conduct. (ECF No. 524, 1-2).

D. Technical Background

The general background to this art involves biologic molecules, and their use as anti-VEGF compounds.

1. The aflibercept molecule and anti-VEGF clinical targets

a. Vascular endothelial growth factor ("VEGF")

In the early 1990s, targeted gene inactivation studies in mice showed that a particular signaling compound in the body called Vascular Endothelial Growth Factor (VEGF) "is necessary for the early stages of vascular development." (DTX 3619.8; DTX 4041.2). In layman's terms, this growth factor stimulates the body to assemble cells to grow new blood vessels. Angiogenesis is the beginning part of that process to signal new blood vessel growth.

VEGF-mediated angiogenesis is a normal part of human functioning. (DTX 4041.2) But too much of the VEGF protein can lead to undesirable effects, such as blood vessel growth for cancerous tumors, or abnormal growth of blood vessels under the retina in the eye, which can lead to fluid leakage or undesirable blood vessel growth in and around the retina. Id.; Tr. 111:5-15

(Yancopoulos); Tr. 280:8-25, 282:18-24, 287:8-17 (Csaky); Tr. 921:18-922:3 (Albini).

By 1993, "Ferrara and colleagues" showed that anti-VEGF antibodies "could inhibit the growth of several human tumor types" in mice; but varying results based on targeting pathways "highlighted the need to optimize blockade of this [VEGF] pathway." (DTX 3592.3). Regeneron's early patents, including one that published in 2000, noted that "[p]ersistent angiogenesis may cause or exacerbate certain diseases such as . . . diabetic retinopathy and neovascular glaucoma. An inhibitor of VEGF activity would be useful as a treatment for such diseases and other VEGF-induced pathological angiogenesis and vascular permeability conditions, such as tumor vascularization." DTX 3619.6, ll. 8-13; see also DTX 3619.36-37 (anti-VEGF compounds are useful for treating "eye disorders such as age-related macular degeneration and diabetic retinopathy")).

VEGF binds to receptors in the body. (Tr. 111:5-9 (Yancopoulos); DTX 3619.5-6). A "portion of the receptor that is displayed on the surface of the cell" is "generally the most distinctive portion of the molecule." (DTX 3619.2). One of these receptors was designated as Receptor 1 ("R1"), another as Receptor 2 ("R2"). PTX 3333.25). "VEGF-R1 binds to VEGF with [the] highest affinity." (Id.) Anti-VEGF compounds were designed to mimic these

receptor binding sites, to capture circulating VEGF before it reaches a receptor in the body. (DTX 4041.3, 5; Tr. 111:18-112:1 (Yancopoulos)).

b. The therapeutic goal and structural rationale for aflibercept

Regeneron identified the therapeutic goal that it sought to solve with its aflibercept molecule: "produce a receptor based VEGF antagonist that has a pharmacokinetic profile that is appropriate for consideration of the antagonist as a therapeutic candidate," and which has "improved pharmacokinetic properties as compared to other known receptor-based VEGF antagonists." (DTX 3619.29-30). Pharmacokinetic properties of the drug are commonly assessed to see how the drug is absorbed, distributed, moves and works, and then eventually metabolizes, through the body. (Tr. 461:2-8 (Furfine)); see, e.g., Persion Pharms. LLC v. Alvogen Malta Operations Ltd., 945 F.3d 1184, 1187 (Fed. Cir. 2019) (noting pharmacokinetic effects included clinical effects such as blood concentration levels of the drug, and side effects associated with administering the drug).

Aflibercept is a man-made protein. (Tr. 448:1-8 (Furfine)). Regeneron disclosed in the prior art that it had prepared anti-VEGF compounds, which had one segment designed to mimic the VEGF binding segments of the R1 and R2 receptors, fused together; and

then an antibody segment, allowing the whole molecule to more strongly bind to VEGF. (DTX 3619.11-14, 16; Tr. 114:1-17 (Yancopoulos); Tr. 448:1-8 (Furfine) ("Aflibercept is a man-made . . . protein where you take two receptors that are normally on the surface of the cell and you genetically engineer them to be on an antibody part" called "the Fc domain," and "that creates a drug")).

The full protein sequence of the R1 receptor "has poor pharmacokinetics that make it difficult to use as a therapeutic agent," so modifying it in the way that Regeneron did (including replacing some parts with parts of the VEGF R2 receptor region) produced a molecule with better pharmacokinetics, including, e.g., VEGFR1R2-FcΔC1(a). (DTX 3619.59-60).

One of the preferred embodiments that Regeneron disclosed was the fusion polypeptide that had "the amino acid sequence set forth in Figure 24A-24C," which was $VEGF_{R1R2}$FcΔCl(a). (DTX 3619.16, 60, 23 ("Figure 24A-24C. Nucleotide and deduced amino acid sequence of the modified FIt1 receptor termed VEGFR1R2FcΔCl(a)")).

Regeneron secured a patent to the aflibercept molecule, the '959 patent, which issued in 2006. (DTX 7.1; Tr. 1432:23-1433:23 (MacMichael)). Example 20 of the '959 patent explains how to prepare VEGFR1R2FcΔCl(a), and provides the complete sequence

across Figures 24A-24C. (DTX 7.73, 29:13:29; DTX 7.63, 9:65-67; DTX 7.42-44).

Regeneron has assigned various descriptors to the molecule known as aflibercept, including VEGF Trap, VEGF Trap-Eye (formulated for use in the eye); and VEGFR1R2FcΔC1(a). (DTX 4008.1, DTX 7.63, 9:65-67, DTX 3592.3 (describing structural features of protein "that we term VEGF Trap"); DTX 4957.5 ("[VEGF Trap-Eye] has been purified and formulated in concentrations suitable for direct injection into the eye."); Tr. 1227:9-12 (Chu 30(b)(6)); Tr. 208:25-209:10 (Yancopoulos); Tr. 1432:8-1438:24 (MacMichael)).

2. Early anti-VEGF performance: non-human data

Before a drug goes into human use, it is required to be tested in preclinical animal models pertaining to the mechanism of action and/or for the disease, and to get a sense of what range of doses will likely work to accomplish the drug's effect. (Tr. 459:2-21, 462:15-465:14 (Furfine)).

a. Establishing aflibercept's anti-angiogenic effect, dose amounts

By 2002, Regeneron published papers in the scientific literature touting aflibercept's potency. In Holash, Regeneron explained its "hope" that "anti-VEGF approaches can be generalized to many different types of cancer, as well as to other diseases in

which pathologic angiogenesis contributes, such as diabetic retinopathy." (DTX 3549.1). Regeneron stated that it had "engineer[ed] a very potent high-affinity VEGF blocker" with "prolonged in vivo" activity, which "lacks nonspecific toxicities, and can effectively suppress the growth and vascularization of a number of different types of tumors in vivo." (Id.) Regeneron reported that its studies using cell lines and rats "indicated that VEGF-Trap$_{R1R2}$ has the potential to be a long-term and potent pharmacologic blocker of VEGF-mediated activities in vivo, far superior to that of parental VEGF-Trap." (DTX 3549.4). Regeneron reiterated that this "combination of high-affinity and improved pharmacokinetics apparently contributes toward making VEGF-Trap$_{R1R2}$ one of the most, if not the most, potent and efficacious VEGF blocker available." (DTX 3549.5; Tr. 114:14-17 (Yancopoulos)).

Much of Regeneron's early work with aflibercept focused on the anti-angiogenic effects of the drug in connection with cancer applications. (Tr. 449:14-16 (Furfine); PTX 3333.27). But Regeneron also assessed the anti-angiogenic effects of aflibercept in animal eyes specific to treating eye disease. In 2003, Saishin et al. reported their results with both subcutaneous and intravitreal injection of aflibercept into mice eyes. (DTX 2751.1; Tr. 1050:24-1051:11, 1080:10-18 (Rabinow)). The authors confirmed that VEGF-TRAP$_{R1R2}$ given as a single intravitreous injection

"markedly suppressed the development of choroidal neovascularization over the course of two weeks." (DTX 2751.7). While the subcutaneous dosing method also produced good results, it required five injections to produce the reported results. (DTX 2751.4; Tr. 1090:5-22 (Rabinow)).

After seeing aflibercept's performance in vivo in mice and rats, the next step was to assess how it performed in primates, and better identify the dose ranges to target. Regeneron specifically assessed which primate doses produced the desired anti-angiogenic effects. (Tr. 1067:9-22 (Rabinow)). Fraser et al. published these results in 2005, reporting among other things "the minimal dose of VEGF $Trap_{R1R2}$ that would be required to interrupt follicular development," which is the time period when angiogenesis occurs, and whether the dose amount impacted the "duration" of the anti-VEGF effect. (DTX 729.2). Fraser reported that the "VEGF $Trap_{R1R2}$ was well tolerated at all doses tested." (Id., 3). The 4 mg/kg and the 1 mg/kg doses "resulted in a significantly longer" period of activity compared to the lower doses. (Id., 5).

In 2005, Regeneron's published patent application reported the results of aflibercept injections into mouse eyes, including intravitreally. (DTX 4229.24 [0031]).

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In U.S. Patent No. 7,303,747 ("the '747 patent"), which published February 9, 2006, and which issued on December 4, 2007, Regeneron characterized the disclosed invention as involving a "therapeutic method for treating or ameliorating an eye disorder," including "age related macular degeneration" and "diabetic retinopathy." (DTX 2730.13, 1:49-54). The compounds preferred to use for this purpose included VEGFR1R2FcΔC1(a). (Id., 1:64-2:2). Regeneron disclosed that the initial dose should be "at least approximately 25-4000 micrograms [4 mg] VEGF inhibitor protein to an affected eye." (Id., 2:14-15; DTX 2730.16, 7:52-55). The '747 patent included preclinical data that tested VEGFR1R2FcΔC1(a), aflibercept, in various retinal models in animals, reporting good results with intravitreal injections. (DTX 2730.13-14 (referencing data in Figures 4-9)). The '747 patent confirms that "[p]referably" the drugs would be administered "directly to the eye," including through "intravitreal injections." (DTX 2730.16, 7:5-10). The aqueous solutions would have "ophthalmically compatible pH and osmolality." (Id., 7:26-28).

The intravitreal injections in the Examples were dosed at 50, 250, or 500 mcg/eye [0.05, 0.25, or 0.5 mg doses/eye]. (DTX 2730.20, 15:2-4). The specification reports that "a single intravitreal injection (500 mcg) [0.5 mg] of VEGFR1R2-FcΔC1(a)

made following the laser injury [to the eye] reduced the incidence of grade 4 lesions from 44% to 0% within 10 days of treatment." (Id., 15:19-23). Example 16 tested VEGFR1R2FcΔC1(a) to assess the "ability of an intravitreally administered protein to reach the desired site of action, i.e. the macula in the case of macular degeneration," and concluded that it would in fact reach "both ocular tissue (vitreous humor, retina and choroid) and that "if a compound is delivered into the vitreous humor, it can be cleared from that region and be distributed into the surrounding tissue, i.e. retina and choroid." (DTX 2730.21-22). The larger VEGF trap protein stayed in the eye tissue longer in comparison to its smaller mini-VEGF trap version. (DTX 2730.22). The specification then proposed treatment in human patient eyes, including that the "eye to be treated is injected with 25-4000 micrograms [4 mg] of VEGF trap protein in an ophthalmic solution." (Id. (Example 17)).

b. Other anti-VEGF compounds: dosing methods

Regeneron closely monitored Genentech, as well as how Genentech planned to dose its anti-VEGF compounds. (See, e.g., Tr. 448:16-449:6 (Furfine); DTX 710.1 (noting Genentech had dosed ranibizumab in rabbits subconjunctivally, intracamerally, and intravitreally)). By March 1, 2004, Genentech reported the

"highest levels [of ranibizumab were] observed for ITV," intravitreal doses. (DTX 710.2).

Genentech compared how ranibizumab performed intravitreally and intravenously in monkeys, confirming by January 2005 that based on the systemic clearance rates, ranibizumab would be "favorable for its clinical use in treating neovascular AMD by monthly ITV injection." (DTX 2265.1; DTX 714.1 (Regeneron calling the Gaudreault paper a "nice find"). Gaudreault likewise evaluated different dosing ranges in primates. (DTX 2265.2 (February 2005 publication by Gaudreault, comparing the performance of intravitreal and intravenous formulations, including 10 mg/mL and 40 mg/mL in 50 microliters dosed intravitreally)).

c. The human clinical activity with anti-VEGF compounds

By 2005, clinicians pursued anti-VEGF strategies, including with intravitreal injections, to treat their patients.

i. The first FDA-approved anti-VEGF agent: Macugen

The anti-VEGF agent, Macugen (pegaptanib), was in Phase I clinical studies as early as April 1999, and had proceeded to Phase II/III studies by 2001. (DTX 209.2-3). In the Phase III studies, "1186 patients were enrolled to test the efficacy of intravitreal injections of pegaptanib every six weeks." (DTX 209.3). By August

31, 2004, Regeneron knew that the FDA's advisory committee had considered the Phase III clinical and safety data, and that "70% of patients met the primary endpoint" of "patients losing less than 15 letters, or three lines, of visual acuity on the eye chart from baseline after 54 weeks." (DTX 209.1, 5). FDA approved Macugen in December 2004. (DTX 4041.1).

ii. Avastin—approved as an anti-VEGF cancer drug, but used by physicians intravitreally to target wet AMD and DME

FDA approved the anti-VEGF Avastin (bevacizumab) as an intravenous anti-cancer therapy in February 2004. (DTX 210.2). By March 3, 2005, the Bascom Palmer Eye Institute issued a press release (which Regeneron received) confirming that it had used Avastin to treat wet AMD. (DTX 210.1; Tr. 1240:22-1242:19 (Chu 30(b)(6))). The study's lead, Dr. Phil Rosenfeld, explained that "[w]e've been injecting anti-VEGF drugs into the eye for the past 3 years with very encouraging results." (DTX 210.1). Dr. Rosenfeld also studied systemic patient dosing because even though "[s]ome people would rather have an injection in the eye than worry about the risks from a systemic drug" systemic dosing would offer "a new potential option for patients with wet AMD." (DTX 210.2). He acknowledged that "the potential disadvantage" of Avastin given systemically was "the risk of systemic side-effects," but

indicated that thus far, patients' blood pressure increases were readily controlled with medication. (Id.)

Shortly thereafter, in July/August 2005, Dr. Rosenfeld and others published further details about their intravitreal Avastin injection process, confirming that Avastin produced efficacious results in a human patient, when injected intravitreally at a concentration of 25 mg/mL. (DTX 3058.2; Tr. 528:2-12 (Furfine); DTX 3510; DTX 2264.1-2; DTX 9036.5-6 (Avery publication from March 3, 2006 dosing 1.25 mg of Avastin in 0.05 mL); DTX 9036.3 (library receipt page showing Avery publication received by March 3, 2006)). The injections were described as "well tolerated in all patients," with no ocular toxicity, "or thromboembolic events," or "significant elevation" in blood pressure "observed over the course of the study." (DTX 2264.3; DTX 9036.7). The "vast majority of patients demonstrated stability or improvement" of their visual acuity," and four weeks after the injections, many "demonstrated complete resolution of retinal edema"; even some non-responders "also showed resolution" after they "received reinjections at week 12." (DTX 2264.3-4; DTX 9036.7-8).

Avery also addressed the theory in the literature that had warned that there might be a "lack of retinal penetration beyond the [internal limiting membrane] after intravitreal administration of full-length antibodies," which was plainly contradicted by "the

apparent rapid biologic effect demonstrated in this current study with bevacizumab." (DTX 2264.8; DTX 9036.12). Avery proposed that the use of a larger dose, human anatomy versus primate anatomy, and the methodology used in the primate studies could account for why the theory did not lead to failure for bevacizumab. (Id.)

Avastin was then tested in clinical trials on extended dosing intervals, with Bashur et al. reporting in 2008 that after three monthly injections, visual acuity gains could be maintained for several months by giving just 3.4 injections on average for the remainder of the year. (DTX 4013.1; Tr. 768:2-10 (Albini)).

iii. Lucentis (ranibizumab)

At the July 2005 American Society of Retinal Specialists meeting," the results from a "large phase Ill clinical trial" demonstrated that ranibizumab was "effective in the treatment of neovascular AMD." (DTX 2264.1-2; DTX 9036.5-6). The active ingredient in Lucentis, ranibizumab, is an antibody fragment. Tr. 2014:5-7 (Trout); Tr 1832:11-1833:1 (Csaky); Tr. 113:7-18 (Yancopoulos); Tr. 452:7-14 (Furfine).

Dr. Rosenfeld presented his one-year PrONTO outcomes at the May 2006 Association for Research in Vision and Ophthalmology ("ARVO") meeting. (DTX 218.2; DTX 3131.3 (dosing patients on a PRN basis after 3 monthly doses)). On May 9, 2006, Regeneron

internally circulated a copy of Dr. Rosenfeld's press release about the study, including that he had dosed ranibizumab using intraocular injections for wet AMD, and that most patients had only needed 5 or 6 injections in the year. (DTX 218.1-2). He reported that "82% of patients had the same or better vision after one year and 35% of patients experienced a two-fold improvement in vision as defined by gaining three lines of vision on a standardized visual acuity chart." (Id., 1). Dr. Rosenfeld did this work even though Lucentis had not yet been officially approved by FDA, and was still being tested in Phase III studies. (Id., 2).

By May 4, 2006, Genentech's patent to Dr. Shams published. Example 1 included a study protocol for the "efficacy and safety of intravitreal injections of VEGF antagonist (e.g., ranibizumab) administered monthly for 3 doses followed by doses every 3 months." (DTX 726.32).

FDA approved Lucentis for wet AMD in June 2006. (See DTX 3040.1). By October 5, 2006, Dr. Rosenfeld and others published the successful Phase III clinical trial results with monthly dosing of ranibizumab for wet AMD in the New England Journal of Medicine. (DTX 2034). Mitchell summarized data for the ANCHOR monthly dosing (2006), PRONTO PRN dosing (2007), and EXCITE quarterly dosing (2008), showing visual acuity gains over many months of time. (DTX

4061.4; see also DTX 3115.1 (Fung, Rosenfeld et al. reported on using OCT to guide extended-interval dosing after three monthly loading doses)).

Once the efficacy of ranibizumab for AMD was established, doctors quickly began using it for other indications, namely DME, DR, and RVO, and also on extended dosing intervals. One review article summarizing DME clinical work included Lalwani 2009, where patients received three monthly doses of ranibizumab (baseline, month 1, month 2), followed by dosing at an extended two month interval, at months 4 and 6, for a mean gain of 8 letters by month 12. (DTX 2733.1; Tr. 768:24-769:14 (Albini)).

iv. Aflibercept

Regeneron initially began its aflibercept work for cancer indications, as part of a partnership with Sanofi. (Tr. 112:19-20 (Yancopoulos); DTX 4956.3-4). Regeneron disclosed that the "results in animal models have supported the exploration of the VEGF Trap in human studies of vascular eye diseases. Initial clinical studies in human patients suffering from both AMD and diabetic edema and retinopathy appear quite promising, with evidence in early trials that the VEGF Trap can rapidly and impressively decrease retinal swelling." (DTX 3592.4)

a) Regeneron tries, and rejects, systemic aflibercept and instead pursues intravitreal aflibercept for human use

Regeneron initiated its first Phase I study with aflibercept through intravenous delivery, by January 2004. (DTX 207.1-2; Tr. 1238:13-19 (Chu)). Like Dr. Rosenfeld, Regeneron initially thought that the ability to dose the drug systemically would be an advantage over direct injection into the eye. (DTX 207.2; DTX 210; Tr. 1240:24-1242:5 (Chu)). Regeneron also secured and published its systemic dosing results in humans in the '747 patent, which published in February 2006. (DTX 2730.23). At the higher 3.0 mg/kg dose group, 2 of the 5 patients experienced adverse events, causing them to all be "prematurely withdrawn from [the] study." (DTX 2730.23, 21:39-22:1)).

Thus, not surprisingly, in its SEC Form 10-K filed in March 2005, Regeneron confirmed its "plan to initiate a clinical trial of the VEGF Trap delivered through intravitreal injection in mid-2005. While use of the VEGF Trap for eye diseases using systemic delivery remains part of our collaboration with sanofi-aventis, we and sanofi-aventis do not currently intend to pursue further clinical development using systemic delivery of VEGF Trap for eye diseases." (DTX 4956.4; id., 119 (publication date March 11, 2005)).

Regeneron additionally released its intravenous aflibercept results for AMD at the ARVO meeting in May 2005. (DTX 211.6-7). Regeneron's briefing document listed its objectives for this 2005 ARVO meeting. Regeneron planned to increase "awareness of the VEGF Trap as [a] promising compound for the treatment of neovascular diseases," (DTX 211.2), reporting that Regeneron had "successfully completed the Phase I study of intravenous VEGF Trap in wet AMD," and identifying the maximum tolerated dose (MTD) for systemic VEGF Trap administration, (id., 3). Regeneron planned to represent that "[n]o unexpected side effects were observed during the systemic Phase I trial," that "[p]roof of concept was obtained for both ITV [intravitreal] and systemic deliveries in a primate model of CNV," and that VEGF Trap had "demonstrated pre-clinical efficacy" when given intravitreally. (Id.) Regeneron also planned to explain that in view of the systemic side effects, it would "continue development with an ITV formulation to maximize VEGF Trap therapeutic benefit," with this "ITV phase 1 study" to begin "this year." (Id.; id., 14 ("ITV formulation chosen to maximize therapeutic benefit"); see also DTX 214.2.

Regeneron also planned to discuss its belief that the intravitreal dosing approach would "allow[] for a longer interval between injections when administered intravitreally," and that "[e]xpansion into other ophthalmic indications including, but not

limited to, diabetic macular edema is also a possibility." (DTX 211.3-4) Copies of the abstracts submitted to ARVO for the May 2005 meeting are at DTX 211.8-13; and are likewise referenced on Dr. Yancopoulos' CV. Thus, Regeneron's intent to dose aflibercept through the intravitreal route to treat eye diseases such as AMD and DME was known to a person of ordinary skill in the art by 2005.

Karen Chu confirmed that the intravitreal dose-ranging study No. 0502, the CLEAR-IT-1 study, was also performed in 2005, and used dose amounts that included 1, 2 and 4 mg, and at 40 mg/mL concentrations. (Tr. 1645:3-1646:21 (Chu); DTX 9005.23). Regeneron announced the results of this dose-ranging study at least by February 2006. (Tr. 1649:5-1650:2 (Chu); DTX 4957.5 ("In February 2006, [Regeneron] announced positive preliminary results from an ongoing Phase I dose-escalation study of the VEGF Trap-Eye")). By March 21, 2006, Regeneron also had submitted its Phase I intravitreal study data, called "CLEAR-IT 1," to the American Society of Retinal Specialists ("ASRS") to present at its meeting in the fall of 2006; Regeneron presented this data again at ARVO in May of 2006. (DTX 216 (confirming ASRS submission); DTX 9006.12 (reference 56); Tr. 1647:11-1648:22 (Chu)). The CLEAR-IT 1 abstract reported that intravitreal injections "of up to 4 mg of VEGF Trap has been well-tolerated." (DTX 216.3; Tr. 1650:7-22 (Chu)).

In early 2006, Regeneron also sought input from key opinion leaders to guide Regeneron's next steps for clinical trial design, including whether clinicians would continue to dose with Avastin, or adopt the PIER loading doses with Lucentis, as well as to seek guidance for how best to dose DME. (DTX 212; DTX 213.1 ("How will Lucentis be used in practice? Monthly . . . Induction followed by quarterly maintenance . . . Induction followed by PRN"; "Will off-label use of Avastin still be rampant after Lucentis is approved"); DTX 213.2 ("How Important is dose frequency?")).

After Dr. Rosenfeld presented his results with less frequent injections with Lucentis from the PrONTO study, Regeneron noted internally that the results "may suggest that the so-called 'clinician prn practice' following 'induction dose' is as good as monthly injections for at least the first year, and that is probably the take home message that the market will follow." (DTX 220.1). Since Lucentis showed effectiveness for 6-8 weeks, Dr. Avner Ingerman suggested that there would be a "potential advantage, of showing comparable efficacy, or even a slightly lower efficacy, and have a win on label dosing interval." (Id.) Dr. Yancopoulos likewise noted that since Lucentis could not last for a full 2 months, this "may provide us [a] major opportunity for VEGF Trap interval advantage!" (DTX 220.2).

By August 2006, Regeneron had reached out to Dr. Rosenfeld to get his input on their VEGF Trap-Eye data, including for DME. Dr. Rosenfeld suggested that Regeneron had a "better probability of showing a more durable treatment effect" compared to Lucentis, and recommended that Regeneron pursue the 2 or 4 mg dose, "which is a 4-fold molar excess over Lucentis with a good chance of better durability," and then dose "every 2 weeks or 4 weeks for a fixed number of doses then see the patients back every 4 weeks and dose as needed." (DTX 222.1). Regeneron's CEO, Len Schleifer, told Dr. Yancopoulos that dosing plans should be finalized "when we know more about our partnering efforts." (Id.)

By February 2007, the European regulatory authorities approved Lucentis with a dosing regimen that included "a loading phase of one injection per month for three consecutive months, followed by a maintenance phase in which patients should be monitored for visual acuity on a monthly basis." (DTX 913.1).

Regeneron discussed with its development partner Bayer its ideas of how aflibercept "could even be better than Lucentis." Tr. 112:7-113:18 (Yancopoulos). As the field recognized, a significant drawback of the primary dosing regimen in Lucentis's label was that it required monthly intravitreal injections of Lucentis, subjecting patients to the very unpleasant experience of having a needle inserted into their eye once a month. See Tr.

129:1-17 (Yancopoulos); Tr. 290:16-291:8 (Csaky). Dr. Yancopoulos thus hoped to develop an aflibercept regimen that would allow the drug to attain either improved patient outcomes, or an extended dosing interval, or both, compared to Lucentis. He sought to reduce "the very significant onerous treatment burden of monthly treatments" and "cut the number of treatments by half," that would "be game-changing for these patients and their caregivers and the doctors." Tr. 124:11-125:1 (Yancopoulos); Tr. 128:9-15 (Yancopoulos).

By March 2007, Dr. Jesse Cedarbaum proposed that in order to "not have to wait for the 80 mg/mL formulation," which had "formulation issues," Regeneron should proceed with the 2 mg dose for the Phase III clinical trials, and that he "could get behind an 8 week interval in place of 12" based on the loss of 8-10 days of half-life exposure due to using the lower dose. (DTX 226.1).

On April 2, 2007, the Regeneron/Bayer joint development team reported a decision to use a dosing regimen of "2mg q8wks w/PlER lead in (dose monthly for 1st 3mths)." (DTX 227.1; Tr. 1258:12-1259:1 (Chu 30(b)(6))). On April 5, 2007, Robert Terifay, Regeneron's head of marketing, noted that having sat with the joint development team to review the CLEAR-IT 2/0508 data, it was clear that "Q8 weeks dosing appears to maintain visual acuity better than Q12 weeks dosing," which justified pursuing the 8-week dosing

interval. He explained the marketing advantages of having a label with an advantage over the Lucentis interval, particularly for drug pricing. (DTX 229.3; DTX 230 (Terifay April 18, 2007 e-mail emphasizing marketing advantages); Tr. 1249:14-19 (Chu (30(b)(6))).

By May 2007, Regeneron released the CLEAR-IT 2 Phase II study data for aflibercept intravitreal injections. (See DTX 232; DTX 234; Tr. 1264:4-1265:15 (Chu 30(b)(6)) (confirming data were presented and public)). Regeneron also published its Phase I DME data, including that its intravitreal injection of a 4 mg dose was "well tolerated" with "no serious drug-related adverse events," and mean BCVA improvements of 2.6 to 6.8 letters by 6 weeks with just a single injection. (DTX 234.3).

Regeneron ultimately submitted to the FDA its Phase III clinical trial plan for 3 monthly doses, followed by every-8-week dosing. FDA announced that the Phase III study would commence in August 2007 on its clinicaltrials.gov website on or around August 1, 2007. (DTX 231.2, 8).

Dixon published that Regeneron's Phase III clinical trials included an arm that had 3 doses given 4 weeks apart, followed by dosing every 8 weeks. (DTX 204.4). Regeneron announced that its Phase III clinical trials met their primary endpoint on November 22, 2010. (DTX 917.1).

v. Design of methods for using anti-VEGF agents

The development of any method of treating angiogenic eye disorders using anti-VEGF agents entails a number of design decisions. The testimony at trial reflected that for any given dosing regimen, the POSA would need to consider the dosage amount, the route of administration, the frequency of administration, the concentration of drug to be administered, whether to use loading doses at the outset of treatment, the number of loading doses to be used, and the duration and frequency of any maintenance doses. Tr. 862:15-863:18 (Albini).

In the context of anti-VEGF therapies, the concept of "loading doses" refers to treatments given one after another, on a fixed schedule, administered unconditionally without personalized decision-making based, for example, on the progression of a patient's disease as measured by Optical Coherence Tomography ("OCT") scans. Tr. 1849:3-25 (Csaky).

The remainder of the treatment schedule (sometimes referred to as the maintenance or extended dosing phase) then can involve various strategies to treat the patient going forward and, ideally, less than monthly injections. For example, in the general time period of 2007-2011, physicians began to make use of a dosing strategy generally called pro re nata ("PRN"), meaning as-needed

dosing. See Tr. 305:18-306:13 (Csaky); Tr. 1877:7-11 (Csaky). PRN dosing generally entailed administering loading doses and then seeing the patient on a fixed schedule going forward (often, but not always, monthly), where the patient would be assessed at regular intervals using an OCT scan that determined whether fluid had begun to reaccumulate in the eye, and then administered a dose of the anti-VEGF agent if fluid had recurred. Tr. 305:18-306:13 (Csaky); Tr. 1819:15-1822:22 (Csaky); DTX-3131 at 11; see also PDX 8.004.

In clinical practice, retina specialists also began using an approach called "treat and extend," in which, following loading doses, the treating physician would attempt to extend the interval for both visits and re-treatment. Tr. 773:16-774-9 (Albini) (describing treat-and-extend). If OCT indicated fluid had recurred at the time of an attempted extended interval visit, the physician would scale back the interval to the prior interval that did not result in the reaccumulation of fluid.

Both PRN and treat-and-extend strategies differ from fixed extended dosing regimens. In the latter, a doctor injects patients at fixed intervals regardless of whether fluid has reaccumulated according to an OCT scan. Tr. 1824:22-1825:6 (Csaky) (fixed extended dosing regimens are "completely different" than OCT-based, individualized retreatment approaches); Tr. 1825:12-25

(Csaky) (fixed approaches differ from personalized approaches); see also Tr. 776:5-20 (Albini) ("there were fixed regimens" and "there were also individualized regimens that sought to evaluate patients and make decisions about whether or not to reinject on a patient basis."); Tr. 835:1-16 (Albini) (distinguishing between PRN treatment and "fixed regimens like monthly dosing"). While PRN and treat and extend treatment methodologies entail "conditional" decisions to retreat a patient, Tr. 1825:3-6 (Csaky), fixed interval strategies do not. Tr. 1825:3-6 (Csaky); Tr. 776:5-20 (Albini); Tr. 781:19-782:7 (PRN dosing means making "decisions . . . whether or not to inject based on clinical measures and imaging findings for that patient") (Albini). The parties agreed that the claims at issue at trial described "loading doses" followed by "subsequent eight-week injections," Tr. 777:25-778:7 (Albini); see Tr. 780:2-10 (Albini) ("eight-week injections"); Tr. 778:20-779:5 (Albini) ("q8-week regular dosing."). Those subsequent eight-week fixed interval injections may be referred to as "maintenance doses" after the initial loading dose treatment phase. Tr. 301:10-23 (Csaky).

vi. Prior Art efforts to develop extended dosing regimens

The parties also largely agreed on a key point at trial: prior to 2011, efforts to attempt fixed extended dosing regimens to

maximize the time that patients could go between intravitreal injections heavily focused on individualized treatment strategies using PRN and treat-and-extend regimens. Tr. 1819:15-20 (Csaky) (personalized approaches were the predominant method for extended dosing prior to 2011); Tr. 875:2-6 (Albini) (most physicians were using personalized approaches in 2010 to 2011). PRN had been widely accepted in light of new OCT technology, which allowed physicians to measure the recurrence of fluid that was believed to contribute to the impairment of vision in connection with angiogenic eye disorders. Tr. 1820:1-19 (Csaky). Dr. Csaky testified at trial that the emergence of OCT technology was critical to the development of personalized treatment strategies, because doctors could measure the fluid re-accumulation in each individual patient and decide whether to retreat or not. Tr. 1822:8-18 (Csaky).

The parties also largely agreed that pre-priority date efforts at fixed extended dosing regimens — i.e., dosing schedules with intervals longer than one month — resulted in worse visual outcomes than monthly and PRN treatment schedules and had largely fallen out of favor. And the unrefuted evidence at trial is that the POSA's goal (like Regeneron's) would have been to improve upon the results that obtained with monthly ranibizumab for treating wet AMD, either in terms of visual acuity gains, or the interval

between doses to spare patients the inconvenience and unpleasantness of injections into the eye. Tr. 1816:4-24 (Csaky) ("[O]ur goals [pre-2011] were . . . to maximize patient's vision," "reduce the number of injections that we were giving to patients to achieve that maximum vision that we could offer them," "reduce the burden on having [patients] come to the office," and "ensure that we were doing these [injections] in a safe way and not exposing patients to undue risks."); Tr. 1822:23-1823:10 (Csaky) (attaining outcomes similar to monthly treatment was what the POSA was aiming for); 123:21-125:1 (Yancopoulos) ("Lucentis set a high bar, but the opportunities were we could either restore more vision or we could do exactly the same as Lucentis but perhaps . . . cut the number of treatments by half . . . ."); see also Tr. 134:21-136:3 (Yancopoulos); 1849:12-25 (Csaky); PTX-3333 at 42, 51. Dr. Yancopoulos testified that in developing his treatment regimen for AMD in particular, he was well aware of the trials that had shown less than promising results using fixed extended dosing regimens at both eight-week and 12-week intervals with ranibizumab. Tr. 130:25-132:5 (Yancopoulos); PTX-3333 at 46-47.

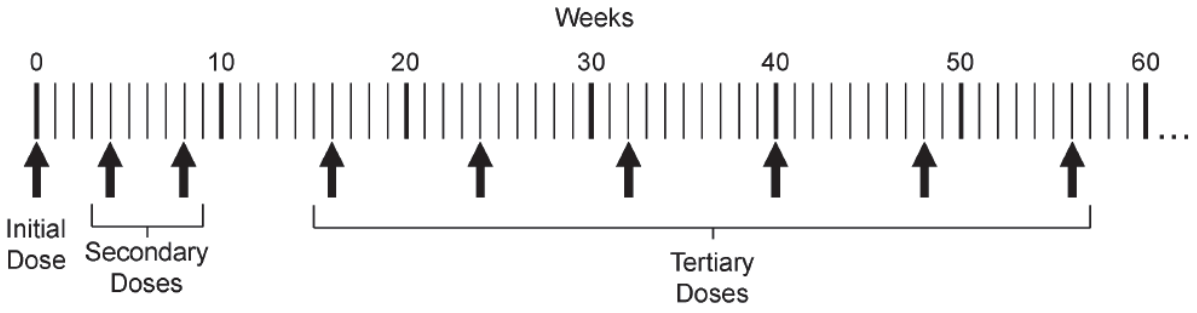
Efforts to achieve a fixed extended dosing regimen before the Treatment Patents' priority date were discouraging. Several clinical trials had tested ranibizumab in wet AMD at extended 12-week fixed dosing intervals following loading doses, with

disappointing results. Tr. 129:18-130-17 (Yancopoulos); Tr. 1916:7-16 (Csaky); PTX-3333 at 46; DTX-4061 at 6 (SAILOR). Most notably, the PIER trial even resulted in an eventual loss of vision for patients once they entered the extended dosing phase. Tr. 872:7-873:15 (Albini); see also PTX-1146 at 8 (EXCITE trial results showing clinical superiority of monthly treatment regimen as opposed to quarterly treatment regimen); DTX-4061 at 6 (SAILOR trial results "indicated that quarterly visits were insufficient to monitor and capture disease progression"). Indeed, even the FDA-approved label for Lucentis notes that dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit." DTX-4056 at 1. PRN dosing regimens, in contrast, had at least resulted in net vision gains, contributing to the uptake of such regimens by physicians in clinical practice. Tr. 1823:11-25 (Csaky). The PrONTO trial, for example, was a well-known clinical trial that helped establish PRN as a recognized method of treating patients with ranibizumab. Tr. 869:25-870:23 (Albini) (PrONTO trial contributed to the "wide adoption of prn dosing back in the 2007-08 time frame"); Tr. 1822:24-1823:25 (Csaky).

Despite PRN's prevalence, the art in the years immediately preceding the January 2011 priority date reflected the POSA's view that the best treatment strategies for wet AMD and DME were unsettled. Both parties cited references describing that

uncertainty, and Defendants' expert, Dr. Albini, agreed that as of 2010 "there was uncertainty as to what the best dosing approaches were for anti-VEGF agents," Tr. 864:6-8 (Albini). One January 2010 article quoted Dr. Csaky as describing dosing approaches for Avastin, for example, as "all seat-of-the-pants," in part because there were no clinical trial-based guidelines. DTX-9014; Tr. 1999:20-2000:23 (Csaky).

Regeneron sought to develop Eylea with the use of extended eight-week fixed dosing regimen. The fixed dosing regimens for aflibercept claimed in the '601 and '572 patents set monthly loading dose periods ("initial" and "secondary" doses) followed by eight-week fixed extended dosing intervals (or "tertiary" doses). Figure 1 of the '601 and '572 patents depicts this concept:



PTX-1 at 10-12, 21-22 ('601 patent); PTX-3 at 13, 15, 25 ('572 patent). It shows an initial loading dose at the beginning of the treatment regimen, two additional loading doses administered at weeks 4 and 8, and the extended fixed dosing intervals every 8 weeks thereafter. PTX-1 at 11-12; PTX-3 at 15. This dosing

regimen and the others claimed in the '601 and '572 patents are not personalized to the individual patient. Tr. 1824:22-1825:6 (Csaky). Physicians do not alter treatment based on an individualized assessment of the patient's vision at any given visit, such as an OCT scan, a clinical examination, or visual acuity measurements. See Tr. 1849:3-18 (Csaky); Tr. 1864:6-11 (Csaky); Tr. 1875:14-1876:5 (Csaky); Tr. 864:18-866:23 (Albini). Instead, physicians treat patients on the "very regimented" schedule as set forth in the Treatment Claims. Tr. 1824:22-1825:6 (Csaky).

In designing its Phase 3 wet AMD trials, for example (the "VIEW 1 and VIEW 2" trials), Regeneron did not know whether its dosing regimen of 2.0 mg of aflibercept using three monthly loading doses, followed by an eight-week fixed extended dosing period would succeed, which is why it included a 2.0 mg monthly regimen as a treatment arm as well. Tr. 134:15-136:3 (Yancopoulos).

vii. Challenges of developing treatment methods for anti-VEGF agents

The parties' experts agreed that drug development is difficult and that the process of developing a drug does not end with the invention of the active molecule. Rather, developers must also create a stable formulation, and then test that drug product by gathering safety and efficacy data during Phase 1, 2,

and 3 clinical trials and beyond. In the context of drugs used to treat angiogenic eye disorders, Phase 1 trials seek "to make sure that nothing terrible happens to the eye" in "a small number of patients," Tr. 1826:17-1827:5 (Csaky), Phase 2 trials seek "to make sure there's a benefit" and "start to decipher a dose and some type of regimen that may or may not give us some ideas of activity," though they "typically are also underpowered," Tr. 1827:6-15 (Csaky), and Phase 3 trials are "the big ones" with "hundreds and hundreds, if not thousands, of patients" that are "able to demonstrate safety and efficacy for the FDA's requirements and then submission to the FDA for approval," Tr. 1827:16-22 (Csaky). The POSA's knowledge of how a drug performs "expands as the number of patients increases in trials over time," and the POSA would know that information from each phase "can either confirm or contradict what you've seen in the preceding phase." Tr. 859:19-860:2 (Albini).

Phase 1 and 2 trials generate "early preliminary data that you try to use to design your definitive Phase 3" trials, "but you can't really count on those numbers and the information that you get there," which is why the FDA demands "not only one large Phase 3 but two large Phase 3 trials to make sure that you see it in very large numbers of patients and you repeat it and confirm it." Tr. 143:7-14, 144:13-145:24 (Yancopoulos). Most drugs "do not

make it through the development process all the way through Phase 3," Tr. 1827:23-1828:6 (Csaky), and other anti-VEGF drugs have failed to demonstrate safety or efficacy during clinical trials and even after FDA approval, see Tr. 1828:7-1829:12 (Csaky). The POSA would have been aware that such a failure could arise at any time. As Defendants' clinical expert Dr. Albini acknowledged, not only can anti-VEGF drugs "get all the way to Phase 3 and still not make it to the market," but "further, a drug can pass Phase 3 and make it into the market and still fail in the real world." Tr. 860:11-861:23 (Albini).

The Court notes, based on the trial record that there was, and may still be, unpredictability in the art that relates to the development of anti-VEGF agents, and improvements in anti-VEGF therapy have not been easy to attain. For instance, both sides' experts referenced the widely recognized failure of another anti-VEGF treatment, Beovu, even after its Phase 3 clinical trials and FDA approval. Tr. 861:6-21 (Albini) (Beovu's significant safety issues only became known after it entered the market); Tr. 1829:6-12 (Csaky) (some patients using Beovu experienced occlusive vasculitis, resulting in blindness). Another anti-VEGF drug, KSI-301, failed its Phase 3 trial. Tr. 860:18-22 (Albini). And even Dr. Albini participated in the clinical trial of a drug called abicipar which also failed after late-stage clinical trials. Tr.

860:23-861:5 (Albini). Efforts to improve drug delivery through a port delivery system also have experienced difficulties. Tr. 1995:14-23 (Csaky) (port delivery system has since been recalled). Indeed, following Eylea's approval in 2011, many years passed before another anti-VEGF therapy was both approved and attained some traction in the market. Tr. 1995:19-23 (Csaky) (FDA approved faricimab in February 2022); Tr. 172:22-24 (Yancopoulos) ("[T]he field was littered with many, many failures, including our own" in the "several attempts to improve on Eylea.").

E. Regeneron's Eylea Product and Methods of Treatment

Regeneron is the holder of BLA No. 125387 for Eylea, which the FDA first approved on November 18, 2011. (ECF No. 494-12, ¶ 12; ECF No. 435, Answer to ¶ 1). As discussed above, Eylea is an ophthalmic drug product invented by Regeneron scientists that has been used to treat millions of patients suffering from diseases that can cause vision loss or even blindness. Tr. 114:21-116:22, 128:2-8 (Yancopoulos); Tr. 282:25-288:9 (Csaky). Specifically, Eylea is indicated for the treatment of patients with angiogenic eye disorders, including Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR), and Retinopathy of Prematurity (ROP).

The active ingredient in Eylea is aflibercept, a fusion protein. Tr. 2012:12-17 (Trout); Tr. 110:14-19 (Yancopoulos); Tr. 448:1-12 (Furfine). Aflibercept works by preventing VEGF from stimulating blood vessel growth in the retina. Tr. 280:6-281:8, 288:10-19 (Csaky); Tr. 110:24-112:1 (Yancopoulos).

After inventing the aflibercept molecule, Regeneron endeavored to develop a safe, effective, and successful ophthalmic drug product. Tr. 172:12-173:22, 184:17-185:7 (Yancopoulos); Tr. 449:19-9 (Furfine). Aflibercept entered into preclinical development in the mid-1990s, and was initially developed as a potential treatment for cancer. Tr. 121:8-12 (Yancopoulos); Tr. 449:14-16, 475:10-17 (Furfine). Its use to treat ophthalmic diseases by injection into the eye was only later considered. Tr. 449:14-21 (Furfine); Tr. 1679:5-1680:11 (Graham). Two of Regeneron's early development partners, Procter & Gamble and Aventis, concluded that an aflibercept-containing product would not be a viable drug product, and abandoned the partnership. Tr. 112:10-113:25 (Yancopoulos). But Regeneron persisted in its efforts to develop a drug that doctors could administer to patients less frequently than the leading treatment at the time, Lucentis. Tr. 2014:5-7 (Trout); Tr 1832:11-1833:1 (Csaky); Tr. 113:7-18 (Yancopoulos); Tr. 452:7-14 (Furfine). Eylea was first approved

by the FDA for the treatment of wet AMD in November 2011. Tr. 214:18-24 (Yancopoulos).

Regeneron's inventors had several aims in developing Eylea. They sought to develop Eylea as a drug for intravitreal injection—i.e., for injection directly into the jelly-like vitreous of the eye. Tr. 288:20-25 (Csaky); Tr. 2034:2-20 (Trout); Tr. 117:15-118:21 (Yancopoulos); Tr. 465:22-466:9 (Furfine). In doing so, Regeneron aimed to develop a drug that was both stable and highly concentrated, thereby delivering large amounts of drug to the eye in a single injection while minimizing the risk of it coming out of solution and causing serious side effects. Tr. 115:1-116:3 (Yancopoulos); Tr. 1680:12-1681:17 (Graham). Although a high concentration could lead to higher efficacy, it also risked instability and adverse effects on patients. Tr. 2044:8-22, 2054:13-15, 2066:10-21 (Trout); Tr. 469:21-471:4, 472:6-19, 473:2-22, 480:6-9 (Furfine); Tr. 1681:18-1682:1, 1691:11-19 (Graham). Among other complications, injecting a drug directly into the eye requires doctors to use exceedingly small, narrow-bore needles that put pressure on drugs—known as shear stress—and can cause the aflibercept protein to come out of solution. Tr. 578:2-9, 2062:9-17, 2066:17-21 (Trout); Tr. 476:2-478:13 (Furfine); Tr. 1683:4-13, 1685:7-15, 1687:3-22, 1688:17-21 (Graham); Tr. 1125:13-16 (Rabinow); Tr. 1465:12-25 (MacMichael).

Because aflibercept is an unnatural fusion protein, not (like other anti-VEGF agents) an antibody or antibody fragment, the inventors did not expect that formulation ingredients that might stabilize an antibody therapeutic would be capable of stabilizing aflibercept. Tr. 573:10-13 (Trout); Tr. 1156:17-24 (Rabinow); Tr. 452:15-454:1 (Furfine). And even if one succeeded in creating a stable, high-concentration formulation of aflibercept, a cloud of uncertainty hung over the whole endeavor: it was unknown whether a protein as large as aflibercept could penetrate through the retinal membrane to an extent that would allow it to enter the retina, the site of action for improving patients' vision. Tr. 2027:14-2028:9 (Trout).

Scientists understood at the time that larger molecules the size of antibodies stayed mostly in the vitreous and did not penetrate the retina, whereas smaller molecules like the antibody fragment ranibizumab were able to penetrate into the retina. Tr. 2027:14-2030:14 (Trout); PTX-1839 at 1 (Gaudreault); PTX-576 at 8-9 (Ghate); PTX-1842 at 1 (Jackson); see also Tr. 455:4-456:24 (Furfine). For precisely that reason, the leading biotechnology company at the time, Genentech, selected a small antibody fragment (ranibizumab), as opposed to a full-sized protein, in developing its intravitreal product Lucentis. Tr. 2026:17-2028:9 (Trout).

Regeneron itself was concerned that aflibercept, originally intended for cancer treatment, was too large to penetrate into the retina, and so undertook a parallel development project involving a smaller protein called "Mini-Trap" as a backup candidate in case the full-length aflibercept proved incapable of sufficiently penetrating into the retina. Tr. 2035:13-2036:17 (Trout); PTX-1757 at 11 (Daly); Tr. 119:1-121:5 (Yancopoulos); Tr. 457:17-458:4, 459:22-25, 461:10-13 (Furfine). In the end, Regeneron unexpectedly demonstrated that aflibercept could penetrate the retina and developed a stable, high-concentration, intravitreal formulation of aflibercept—which eventually became the commercial Eylea formulation. Tr. 466:22-467:9, 495:15-496:17 (Furfine). The Eylea formulation contains 40 mg/ml aflibercept, 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2.

Regeneron also sought to develop a clinical regimen superior to Lucentis's monthly dosing regimen, one that would reduce the number of injections that patients had to receive. Tr. 116:7-22, 128:9-132:5 (Yancopoulos). Intravitreal injection into the eye is burdensome for patients and their caregivers, and entails serious risks—including infection, inflammation, and retinal detachment, as well as anxiety and discomfort. Tr. 291:22-295:8 (Csaky). Although Lucentis provided significant benefit to patients

compared to previous therapies, the need to administer it every month to patients by intravitreal injection posed an onerous treatment burden; a drug product that could be administered less frequently would constitute a benefit for patients. Tr. 307:16-309:1, 334:12-337:25, 1816:4-24 (Csaky); see also Tr. 129:18-132:5, 137:3-21 (Yancopoulos). Regeneron's co-founder and Chief Scientist, Dr. George Yancopoulos, sought to reduce that "very significant onerous treatment burden of monthly treatments" and "cut the number of treatments by half," which would "be game-changing for these patients and their caregivers and the doctors." Tr. 124:11-125:1 (Yancopoulos); Tr. 128:9-15 (Yancopoulos). Ultimately, Dr. Yancopoulos invented fixed, extended-dosing regimens for aflibercept, and Regeneron obtained FDA approval for Eylea using these regimens. Tr. 303:6-304:25, 308:23-309:20 (Csaky); PTX-917 at 1 (Eylea Label); PTX-1 & PTX-3 (Treatment Patents); see also Tr. 133:10-13, 137:3-21, 153:4-8 (Yancopoulos).

F. The Patents-in-Suit and Asserted Claims

The '865 Patent, also referred to as the "Product Patent," covers formulations of aflibercept such as Eylea. The '601 and the '572 Patents, also referred to as the "Treatment Patents," are directed to methods of using aflibercept.

1. The '865 Patent

The '865 Patent was issued by the United States Patent and Trademark Office ("USPTO") on August 10, 2021. The title of the '865 Patent is "VEGF Antagonist Formulations Suitable for Intravitreal Administration." The '865 Patent lists Eric Furfine, Daniel Dix, Kenneth Graham, and Kelly Frye as the inventors. The '865 Patent issued from U.S. Patent Application No. 16/739,559, which was filed on June 10, 2020. Regeneron is listed as assignee on the face of the '865 Patent. The '865 Patent on its face claims priority and/or benefit to U.S. Provisional Application No. 60/814,484, which was filed on June 16, 2006. The '865 Patent lists nine other patents that, as of the issue date of the '865 Patent, had issued from the same patent family.

Regeneron asserts claims 4, 7, 9, 11, and 14-17 of the '865 Patent. The asserted claims depend from claims 1 and 2 which provide as follows:

> 1. A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:
>
> a vascular endothelial growth factor (VEGF) antagonist,
> an organic co-solvent,
> a buffer,
> and a stabilizing agent,
>
> wherein said VEGF antagonist fusion protein is glycosy- lated and comprises amino acids 27-457 of SEQ ID NO:4; and

> wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.
>
> 2. The vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

PTX 2.19. Claim 4 is illustrative. If the Defendants Infringe claim 4, then they necessarily infringe the other asserted claims. Claim 4 states: "The vial of claim 2, wherein said organic co-solvent comprises about 0.03% to about 0.1 % polysorbate 20." PTX-2.19.

2. The '601 Patent

The '601 Patent was issued by the USPTO on January 12, 2021. The title of the '601 Patent is "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders." The '601 Patent lists George Yancopoulos as the inventor. The '601 Patent issued from U.S. Patent Application No. 16/397,267, which was filed on April 29, 2019. Regeneron is listed as assignee on the face of the '601 Patent.

The '601 Patent on its face claims priority and/or benefit to U.S. Provisional Application No. 61/432,245, which was filed on January 13, 2011; U.S. Provisional Application No. 61/434,836,

which was filed on January 21, 2011; U.S. Provisional Application No. 61/561,957, which was filed on November 21, 2011; PCT/US2012/020855, which was filed on January 11, 2012; and U.S. Patent Application No. 13/940,370, filed on July 12, 2013, among additional U.S. Patent Applications. The '601 Patent lists three other patents that, as of the issue date of the '601 Patent, had issued from the same patent family.

Regeneron asserts claim 11 of the '601 Patent which depends from claim 10:

> 10. A method for treating diabetic macular edema in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.
> 11. The method of claim 10, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

PTX 1.21.

Regeneron also asserts claim 19 of the '601 Patent which depends from claim 18.

> 18. A method for treating diabetic retinopathy in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.
> 19. The method of claim 18, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

PTX 1.22.

3. The '572 Patent

The '572 Patent was issued by the USPTO on February 22, 2022. The title of the '865 Patent is "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders." The '572 Patent lists George Yancopoulos as the inventor. The '572 Patent issued from U.S. Patent Application No. 17/352,892, which was filed on June 21, 2021. Regeneron is listed as assignee on the face of the '572 Patent.

The '572 Patent on its face claims priority and/or benefit to U.S. Provisional Application No. 61/432,245, which was filed on January 13, 2011; U.S. Provisional Application No. 61/434,836, which was filed on January 21, 2011; U.S. Provisional Application No. 61/561,957, which was filed on November 21, 2011; PCT/US2012/020855, which was filed on January 11, 2012; and U.S. Patent Application No. 13/940,370, filed on July 12, 2013, among additional U.S. Patent Applications. The '572 Patent lists six other patents that, as of the issue date of the '572 Patent, had issued from the same patent family.

Regeneron asserts claim 6 of the '572 Patent which depends from claims 1, 2, and 3:

> 1. A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary

doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;

wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

2. The method of claim 1 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

3. The method of claim 2 wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

6. The method of claim 3 wherein the aflibercept is formulated as an isotonic solution.

PTX 3.25.

Regeneron also asserts claim 25 of the '572 Patent which depends from claim 15:

15. A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

25. The method of claim 15 wherein four secondary doses are administered to the patient.

PTX 3.25.

G. Claim Construction

1. The Product Patent

In the course of this litigation, the parties stipulated that the term "glycosylated" in claim 1 of the Product Patent is construed as "containing at least one amino acid residue with an attached carbohydrate." During claim construction, they submitted several claim terms from the Product Patent for construction by the Court, "organic co-solvent" and "native conformation." The Court construed "organic co-solvent" to mean "an organic substance added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist." (ECF No. 427 at 20). The Court construed "native conformation" to mean "the original intact form of the VEGF antagonist, which is a form that does not exhibit chemical or physical instability." Id. at 25-26.[4] The Court applies its prior constructions to these claim terms and applies the "ordinary and customary" meaning as understood by a person of ordinary skill in the art to the remaining claim terms. See

[4] The Court also found that the claim term "[w]herein the exclusion criteria for the patent include. . . ," as used in the '601 Patent and the '865 Patent to lack patentable weight. (ECF No. 427 at 29-37).

Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).

2. The Treatment Patents

Certain language in claims 11 and 19 of the '601 Patent and claims 6 and 25 of the '572 Patent, collectively referred to as the "Treatment Claims," relates to the visual acuity outcomes measured by doctors in the patients they treat. During claim construction, the Court construed these visual acuity limitations to lack patentable weight. (ECF No. 427 at 37–39).

The Court applies its prior constructions to these claim terms herein. Accordingly, it affords no patentable weight to the following language of claims 1, 2, and 3 of the '572 Patent, all of which are incorporated by virtue of dependency into claim 6 of the '572 Patent:

- "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose";
- "wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score"; and
- "wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score."

The Court does not consider the visual acuity limitations included in claims 1, 2, and 3 of the Angiogenic Eye Disorder Claim in its infringement or validity analyses, because it has concluded that those are not entitled to patentable weight. (ECF No. 427 at 37-39). The Court applies the "ordinary and customary" meaning as understood by a person of ordinary skill in the art to the remaining claim terms. Phillips, 415 F.3d at 1313.

H. The Defendants' BLA and Yesafili Product

Mylan submitted BLA No. 761274 to FDA on October 29, 2021. Tr. 309:21-310:6 (Csaky). Mylan later transferred its rights in the Yesafili BLA to Biocon, a biopharmaceutical company based in India. (ECF No. 523 at 1-2; Tr. 310:7-15 (Csaky)). By stipulation of the parties, Biocon was then added to this case as a Defendant-Counterclaim Plaintiff. (ECF No. 523 at 2). If Yesafili is eventually marketed in the United States, it will be sold by Biocon. Tr. 310:13-15. The parties stipulated, and the Court ordered, that any evidence that supports a finding of patent infringement as to Mylan will support a finding of patent infringement as to Biocon. (ECF No. 523 at 2).

[redacted]

****SEALED****

MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

[redacted] The Defendants' BLA seeks FDA approval to market an aflibercept biologic product under the trade name Yesafili. (ECF No. 523, 1; ECF No. 494-12, ¶¶ 1, 41). BLA No. 761274 seeks FDA licensure of Yesafili pursuant to 42 U.S.C. § 262(k)(4) for each of the following angiogenic eye disorders: neovascular age-related macular degeneration ("wet AMD"), macular edema following retinal vein occlusion ("RVO"), diabetic macular edema ("DME"), and diabetic retinopathy ("DR").

The Defendants' BLA also specifies the composition of Yesafili. PTX-1541. The [redacted] drug product for BLA No. 761274 comprises [redacted] M710, [redacted] histidine, [redacted] histidine hydrochloride monohydrate, [redacted] polysorbate 20, [redacted] trehalose dihydrate and water for injection q.s. to 0.05 mL. Like Eylea, Yesafili's active ingredient is aflibercept at a target concentration of 40 mg/ml. PTX-1541; Tr. 584:7-12, 587:13-588:5 (Trout). In the composition of the M710 drug product, the Defendants' BLA identifies [redacted]

[redacted]

5 [redacted]

[redacted]

The Defendants' Yesafili BLA also includes a proposed label to be packaged along with the marketed product. Tr. 310:16-311:13 (Csaky); PTX-3097 (Mylan label dated August 2022); PTX-3338 (Biocon label). That label contains no material differences from the label that Regeneron includes with its Eylea product. Tr. 313:7-22 (Csaky); PTX-917 (Regeneron's Eylea label). In particular, there is no difference in how Regeneron's label recommends that doctors use Eylea to treat AMD, DME, and DR as compared with how the Defendants' proposed label recommends that doctors use Yesafili to treat AMD, DME, and DR. Tr. 313:18-22 (Csaky).

I. Prior Art

The parties have stipulated the following regarding the prior art:

"VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration," by J.A. Dixon et al. ("Dixon"), published in 2009.

"An Exploratory Study of the Safety, Tolerability and Bioactivity of a Single Intravitreal Injection of Vascular

Endothelial Growth Factor Trap-Eye in Patients with Diabetic Macular Edema," by D. Do et al, ("Do 2009") published in 2009.

"Anti-VEGF Therapy in Diabetic Macular Edema: An Overview of New Agents Under Investigation," by G. Lalwani ("Lalwani 2009") published in 2009.

"Enrollment Completed in Regeneron and Bayer Healthcare Phase 2 Studies of VEGF Trap-Eye in Neovascular Age-Related Macular Degeneration (Wet AMD)," ("9-14-2009 Press Release") is a press release publicly distributed by Regeneron Pharmaceuticals, Inc. on September 14, 2009.

U.S. Patent No. 7,303,747 issued December 4, 2007, and claims priority to a June 8, 1999 provisional patent application.

"Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function," by H.M. Fraser et al. ("Fraser") published in February 2005.

"VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects," by J. Holash et al. ("Holash" or "Holash 2002") published in August 2002.

"Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2," by C. Wulff et al. ("Wulff") published in July 2002.

Patent Application No. WO 00/75319 ("Papadopoulos") published in 2000.

"Physical Stability of Proteins in Aqueous Solution: Mechanism and Driving Forces in Nonnative Protein Aggregation," by Chi et al. ("Chi") published in September 2003.

U.S. Patent No. 10,406,226 ("the '226 patent") claims priority to a U.S. Provisional Application filed March 25, 2005.

U.S. Patent No. 8,110,546 ("Dix") claims priority to a U.S. Provisional Application filed March 25, 2005.

U.S. Patent Application Publication No. US2001/0014326 ("Andya '326") published on August 16, 2001.

U.S. Patent Application Publication No. US2004/0197324 ("Liu") published on October 7, 2004.

Patent Publication No. WO 2006/047325 ("Shams") published May 4, 2006.

"Preclinical Pharmacokinetics of Ranibizumab (rhuFabV2) After a Single Intravitreal Administration," by J. Gaudreault et al. ("Gaudreault") published in February 2005.

Patent Publication No. WO 97/04801 ("Andya '801") published on February 13, 1997.

U.S. Patent No. 9,340,594 ("'594 patent") issued from the same family from which the '865 Patent issued.

U.S. Patent No. 9,580,489 ("'489 patent") issued from the same family from which the '865 Patent issued.

U.S. Patent No. 7,608,261 ("'261 patent") issued from the same family from which the '865 Patent issued.

J. Trial Witnesses

The parties presented live testimony from the following witnesses, listed in alphabetical order, at trial.

1. Dr. Thomas Albini

Dr. Thomas Albini is an ophthalmologist and vitreoretinal surgeon who received his medical degree from the Johns Hopkins University School of Medicine; he completed an ophthalmology residency at the Doheny Eye Institute at the University of Southern California and is currently a Professor of Ophthalmology at the Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine. (Tr. 748:7-749:3 (Albini)). Dr. Albini is a member of, and serves on committees of, the Retina Society and the Macula Society, is a founding member of the Vit-Buckle Society, serves as co-director of the annual Angiogenesis meeting, and has served as an editor for the Journal of Vitreoretinal Diseases and Retina Today. (Tr. 751:2-752:4 (Albini)). Dr. Albini was qualified without objection as an expert in the diagnosis and treatment of vitreoretinal disease. (Tr. 754:18-755:11 (Albini)).

2. Abby Cahn

Abby Cahn is Regeneron's Marketing and Customer Engagement Executive Director and was designated as a 30(b)(6) witness concerning Regeneron's marketing of Eylea. (Tr. 951:9-12, 22-24 (Cahn (30(b)(6)); see also DTX 802.3). She was presented by designated video deposition testimony.

3. Dr. Hana Chang

Dr. Hana Chang is a research scientist who was formerly employed by a third-party company, Integrity Bio. (ECF No. 543, 2). [redacted] Dr. Chang was presented by designated video deposition testimony.

4. Karen Chu

Karen Chu has worked at Regeneron for the past twenty years and currently serves as Regeneron's Executive Director of Clinical Strategy and Execution for Ophthalmology. Tr. 1583:5-1912, 1586:6-8 (Chu). In that role, she oversees "all of ophthalmology clinical development," including "the design, strategy, and execution of clinical trials." Tr. 1583:13-19. As Ms. Chu testified, she was involved with the clinical development of Eylea

from the time it first entered clinical trials. Tr. 1586:19-25. She testified in her personal capacity about the history of Eylea's clinical development as well as Dr. Yancopoulos's involvement in the Eylea development program.

Regeneron also designated Chu as a Rule 30(b)(6) deponent on a variety of topics, including Regeneron's clinical trials, secondary considerations, and the conception and reduction to practice of the claimed inventions. (DTX 202.1; Tr. 1225:23-1227:14, 1230:6-10 (Chu (30(b)(6)); see also DTX 802.3). Her 30(b)(6) testimony was presented by designated video deposition.

5. Jenifer Colyer

Jennifer Colyer is Regeneron's Executive Director of Commercial Finance and Business Planning. (Tr. 971:14-16 (Colyer 30(b)(6))). Regeneron designated Ms. Colyer as a 30(b)(6) witness to testify concerning Eylea marketing and financial data, including Eylea sales information. (DTX 501.1; Tr. 969:7-18 (Colyer 30(b)(6)); see also DTX 802.3). She was presented by designated video deposition testimony.

6. Dr. Karl Csaky

Dr. Karl Csaky, M.D., Ph.D., is a physician who studies and cares for patients with diseases of the retina. Tr. 268:3-15 (Csaky). Dr. Karl Csaky is a retinal specialist and vitreal retinal surgeon who received his medical degree from the University

of Louisville and completed an ophthalmology residency at Washington University in St. Louis (Tr. 268:3-15, 270:16-18, 271:4-12, (Csaky)). Dr. Csaky currently works at a "not-for-profit academic research institution" called the Retina Foundation of the Southwest in Dallas, Texas, where he holds the titles Chief Executive Officer, Chief Medical Officer, and T. Boone Pickens Director of the Molecular Ophthalmology Laboratory and Clinical Center of Innovation for Macular Degeneration. Tr. 269:12-270:6. Dr. Csaky is involved with the Macula Society, the Retina Society, the American Society of Retina Specialists, and the American Ophthalmologic Society, and serves on several committees, as well as training fellows and publishing in the area of angiogenic eye disorders. (Tr. 275:11-276:22 (Csaky)).

For the past thirty years, Dr. Csaky has treated patients with retinal diseases, including AMD, DME, and DR, and has done so using Eylea. Tr. 268:16-20, 274:16-275:10. About half of his more than 140 publications relate to such retinal diseases. Tr. 276:17-22. Dr. Csaky has run and helped organize clinical trials, including working closely with FDA on the design of clinical trials. Tr. 277:1-9. Dr. Csaky was qualified without objection as an expert in ophthalmology with a specialty in angiogenic retinal diseases and their treatment. (Tr. 277:20-278:1 (Csaky)).

7. Dr. Eric Furfine

Dr. Eric Furfine is the former head of preclinical development at Regeneron; and is a named co-inventor of the '865 Patent. (Tr. 443:7-10, 445:20-446:5, 446:12-21 (Furfine)). Dr. Furfine serves as Chief Scientific Officer and Chief Executive Officer of Mosaic Biosciences, providing scientific services to small biotech companies. Tr. 443:7-16 (Furfine). From 2002 through 2006, Dr. Furfine led Regeneron's preclinical development efforts, including protein formulation development and early animal studies. Tr. 445:1-4, 445:22-446:5. Dr. Furfine testified about his work at Regeneron on the Eylea product, including his efforts to develop the Eylea formulation covered by the claims of the Product Patent.

8. Dr. Parag Goyal

Dr. Parag Goyal is a former Mylan employee who was a Senior Director, Biologics R&D at Mylan, Inc., and who was designated as Mylan's Rule 30(b)(6) witness regarding certain aspects of the development of Mylan's aflibercept product. (ECF No. 543, 22). He was presented by designated video deposition testimony.

9. Dr. Kenneth Graham

Dr. Kenneth Graham is a senior director in a formulation development group at Regeneron, and is a named co-inventor of the '865 Patent. (Tr. 1671:24-1672:2, 1678:17-19 (Graham)). Dr. Graham has worked at Regeneron for more than twenty-two years; he

currently serves as a Senior Director overseeing a formulation-development team at Regeneron. Tr. 1671:20-1672:2 (Graham). Dr. Graham testified about his efforts to develop and test stable formulations of aflibercept for intravitreal injection, culminating in the stable formulation of Regeneron's Eylea product, which is covered by the Product Patent.

10. Dr. Gregory MacMichael

Gregory MacMichael, Ph.D., is a consultant with experience in the biopharmaceutical industry. Tr. 1369:21-24, 1371:12-18 (MacMichael). He was accepted as an expert in the formulation and development of therapeutic proteins. Id.

11. Dr. Barrett Rabinow

Dr. Barrett Rabinow received his Ph.D. in physical organic chemistry from the University of Chicago; earned the title of Baxter Distinguished Scientist after nearly 40 years of employment at Baxter Healthcare Corporation; and is currently a pharmaceutical consultant. (Tr. 1000:22-1001:2, 1001:16-21, 1004:2-18 (Rabinow)). He was qualified without objection as an expert in pharmaceutical formulation science, including the development and manufacture of therapeutic protein formulations. (Tr. 1005:9-16 (Rabinow)).

12. Vanessa Smith

Vanessa Smith is Mylan's Director of Core Regulatory Labeling Strategy, who was designated as Mylan's Rule 30(b)(6) witness on the topic of labeling. (ECF No. 538-3, 8). She was presented by designated video deposition testimony.

13. Dr. Jay Stewart

Dr. Jay Stewart is an ophthalmologist and retinal specialist who received his medical degree from Harvard; is a full professor with the University of California San Francisco medical school, and Chief of Ophthalmology at SF General Hospital. (Tr. 1267:13-1268:16 (Stewart)). He serves as the Editor-in-Chief for the American Journal of Ophthalmology Case Reports and Associate Editor-in-Chief for Annals of Eye Science. (Tr. 1269:2-6 (Stewart)). He was qualified without objection as an expert in the medical and surgical treatment of vitreoretinal and ophthalmic diseases. (Tr. 1270:9-15 (Stewart)).

14. Dr. Bernhard Trout

Dr. Bernhardt Trout received his Ph.D. in chemical engineering from the University of California, Berkeley, and is a Professor of Chemical Engineering at the Massachusetts Institute of Technology. (Tr. 567:4-18 (Trout)). At MIT, Dr. Trout performs pharmaceutical development and manufacturing research on biologic (e.g., protein-based) therapeutics and small-molecule

therapeutics. Tr. 568:2-6. Since 1998, Dr. Trout has worked on approximately fifty biologic therapeutics. Tr. 568:14-2420. He has experience working with bevacizumab, a protein-based drug that is injected into the eye. Tr. 568:21-24. Dr. Trout teaches undergraduate students, graduate students, and post-doctoral researchers on fundamental aspects of chemical engineering. Tr. 569:3-7. He also teaches an annual course to professionals from the biopharmaceutical industry on the subject of biologic molecule formulations ("bioformulation"). Tr. 569:8-23. Dr. Trout regularly consults with industry and government officials, including FDA and foreign regulatory agencies. Tr. 569:24-570:16. He has authored more than two hundred publications, including more than fifty in the field of protein formulation. Tr. 570:17-23. He was qualified without objection as an expert in formulation and stabilization of protein and small-molecule therapeutics. (Tr. 571:24-572:5 (Trout)).

15. Dr. George Yancopoulos

Dr. Yancopoulos is the co-founder, co-chairman, President, and Chief Scientist at Regeneron. Tr. 97:7-9 (Yancopoulos). In his role as Chief Scientist, Dr. Yancopoulos oversees all aspects of biopharmaceutical research and development at Regeneron. Tr.

97:10-13. He is listed as the sole named inventor of the '572 and '601 Patents. (Tr. 100:7-101:21 (Yancopoulos)).

Dr. Yancopoulos testified on background regarding Regeneron, and its various research and development efforts over the years with aflibercept. (Tr. 97:14-99:17, 107:11-108:2, 108:7-109:16 (Yancopoulos)). Dr. Yancopoulos explained his early interest in science and his role in developing Regeneron from a small startup to one of the world's leading biopharmaceutical companies. Tr. 102:20-110:10. Dr. Yancopoulos testified about his involvement in the development of Eylea, including his work leading to the methods of treatment claimed in the Treatment Patents.

Dr. Yancopoulos is the named inventor on more than 150 patents, is an author of more than 500 scientific publications, and has been recognized as one of the top scientists in the world based on citation index. Tr. 100:10-12, 102:3-6, 102:16-19. He was elected to the National Academy of Sciences and to the Biotech Hall of Fame; selected by Ernst & Young as Entrepreneur of the Year; and recognized by Forbes Magazine as one of the Heroes of the Pandemic. Tr. 102:7-15. Dr. Yancopoulos acknowledged that he is not a formulator, (Tr. 216:13-16 (Yancopoulos)), or practicing ophthalmologist, (Tr. 242:17-19, 252:6-9 (Yancopoulos)); he has further earned in excess of $100 million off the value of Regeneron. (Tr. 251:23-252:5 (Yancopoulos)).

III. CONCLUSIONS OF LAW

A. Person of Ordinary Skill in the Art

In a patent case, the overall framework for analysis is presented in the context of a hypothetical person of ordinary skill in the art ("POSA"). Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985). This legal construct is "akin to the 'reasonable person' used as a reference in negligence determinations. The legal construct also presumes that all prior art references in the field of the invention are available to this hypothetical skilled artisan." In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). Courts may also account for "the inferences and creative steps that a person of ordinary skill in the art would employ." Id. at 418.

Determining who constitutes a person of ordinary skill in the art ("POSA") is a factual question. See ALZA Corp. v. Andrx Pharm., LLC, 603 F.3d 935, 940 (Fed. Cir. 2010). To determine the level of ordinary skill in the art, courts consider the following non-exhaustive factors: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which

innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." Daiichi Sankyo Co., Ltd. v. Apotex, Inc., 501 F.3d 1254, 1256 (Fed. Cir. 2007).

1. The Product Patent

The parties advanced substantially similar definitions of a POSA to whom the '865 Patent is directed. According to Regeneron, the POSA "would be a professional with a master's degree at least in a relevant field, so a technical field directly relevant to formulations here." Tr. 2092:6-17 (Trout); PDX-9.002 (explaining that the POSA "would have held an advanced degree, such as a Master's in a biopharmaceutical science, or a related discipline, such as chemical engineering, and several years of experience in the development of biologics products. Alternatively, the POSA could have a Ph.D. in such discipline and less experience. The POSA may collaborate with others, including a medical doctor with experience treating ophthalmic diseases."). According to the Defendants, the POSA would have a similar but somewhat higher level of skill: "at least a PhD in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins or a lower degree with more

practical industrial experience." Tr. 1372:25-1373:14 (MacMichael).

The parties agree that there is no significant difference between these definitions that would impact the Court's examination of the '865 Patent. The Court adopts Regeneron's less-stringent definition of the POSA for purposes of this opinion. However, its opinion would be no different were it to perform the required analysis under the Defendants' definition of the POSA.

2. The Treatment Patents

The parties likewise offered substantially similar definitions of a POSA to whom the '601 and '572 Patents are directed. Regeneron offered the following definition of the POSA as relates to the Treatment Claims:

> A person of ordinary skill in the art relevant to the claims is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists, and would have access to individuals with experience with intravitreal injection formulations.

Tr. 1815:13-1816:3 (Csaky).

The Defendants offered a slightly different definition of the POSA with respect to the Treatment Claims, stating that they would have:

> 1. Knowledge regarding the diagnosis and treatment of angiogenic eye disorders,

including the administration of therapies to treat said disorders; and

2. The ability to understand results and findings presented or published by others in the field, including the publications discussed herein.

Typically, such a person would have an advanced degree, such as an MD or PhD, or equivalent or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field with practical academic or medical experience in:

1. Developing treatments for angiogenic eye disorders, such as AMD, including through the use of VEGF antagonists; or

2. Treating of same, including through the use of VEGF antagonists.

Tr. 752:17-753:13 (Albini).

Neither party has presented any substantive difference between these two definitions as dispositive or critical to resolution of any issue in the case. Nevertheless, because one of the Treatment Claims involves formulation as an isotonic solution ('572 Patent, claim 6), the Court concludes that Regeneron's definition of the POSA is most appropriate to the claims at issue and adopts it for purposes of this opinion. However, the Court finds that its opinion would be no different were it to perform the required analysis under the Defendants' definition of the POSA.

B. Infringement of the Patents-in-Suit

Regeneron contends that the Defendants have infringed the Product Patent because Yesafili meets each of the asserted claim limitations. The Defendants dispute that Yesafili infringes the Product Patent because the polysorbate in their formulation is not an "organic co-solvent" as the claim has been construed by the Court.

Regeneron further asserts that the Defendants will induce infringement of the asserted claims of the Treatment Patents because the proposed Yesafili label copies the Eylea label and instructions physicians to carry out the claimed methods of treatment. The Defendants, however, contend that Regeneron has failed to demonstrate that physicians will use Yesafili in a manner that constitutes direct infringement and has failed to demonstrate that the Defendants specifically intended to induce infringement.

1. Legal Standard

"[W]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). "The patentee bears the burden of proving infringement by a preponderance of the evidence." Creative Compounds, LLC v. Starmark Lab'ys, 651 F.3d 1303, 1314 (Fed. Cir. 2011) (quoting SRI

Int'l v. Matsushita Elec. Corp., 775 F.2d 1107, 1123 (Fed. Cir. 1985)). "An infringement analysis entails two steps. The first step is determining the meaning and scope of the patent claims asserted to be infringed. The second step is comparing the properly construed claims to the device accused of infringing." Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc) (citation omitted). The first step is a question of law, id. at 979, while the second step is a question of fact. Spectrum Pharms., Inc. v. Sandoz Inc., 802 F.3d 1326, 1337 (Fed. Cir. 2015); see also Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd., 887 F.3d 1117, 1125 (Fed. Cir. 2018) ("In a bench trial," whether the BLA infringes "is a question of fact.").

Under 35 U.S.C. § 271(e)(2)(A), when a party submits a regulatory submission to the FDA that describes "a drug claimed in a patent," this can constitute an infringing act under certain circumstances. In re Brimonidine Pat. Litig., 643 F.3d 1366, 1377 (Fed. Cir. 2011). Like the Hatch-Waxman Act for an ANDA filing, and under the BPCIA for a BLA filing, the submission to the FDA constitutes a hypothetical "artificial" or a "technical" act of infringement. Sandoz, 582 U.S. at 10; Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc., 731 F.3d 1271, 1278 (Fed. Cir. 2013).

An infringement inquiry provoked by a regulatory filing must be "focused on a comparison of the asserted patent against 'the

product that is likely to be sold following [BLA] approval.'" Alcon Rsch. Ltd. v. Barr Lab'ys, Inc., 745 F.3d 1180, 1186 (Fed. Cir. 2014). "[I]f a product that an . . . applicant is asking the FDA to approve . . . falls within the scope of an issued patent, a judgment of infringement must necessarily ensue." Sunovion Pharm., Inc., 731 F.3d at 1278.

a. Literal Infringement

"Literal infringement requires the patentee to prove that the accused device contains each limitation of the asserted claim(s)." Bayer AG v. Elan Pharm. Rsch. Corp., 212 F.3d 1241, 1247 (Fed. Cir. 2000). "If even one limitation is missing or not met as claimed, there is no literal infringement." Mas-Hamilton Grp. v. LaGard, Inc., 156 F.3d 1206, 1211 (Fed. Cir. 1998).

b. Induced Infringement

"To succeed on a theory of induced infringement, the plaintiff is required to prove by a preponderance of the evidence (1) direct infringement, i.e., if defendant's drug was 'put on the market, it would infringe the relevant patent'; and (2) 'that [defendant] possessed the specific intent to encourage another's infringement.'" Genentech, Inc. v. Sandoz Inc., 55 F.4th 1368, 1376 (Fed. Cir. 2022) (quoting Vanda, 887 F.3d at 1129–30). "This requires a plaintiff to show that the alleged infringer's actions induced infringing acts and that he knew or should have known his

actions would induce actual infringements." GlaxoSmithKline v. Teva Pharm., 7 F.4th 1320, 1327 (Fed. Cir. 2021).

Specific intent may be shown if the defendant's proposed label recommends, encourages, or promotes an infringing act or through other circumstantial evidence. Genentech, 55 F.4th at 1376; GlaxoSmithKline, 7 F.4th at 1327. When a plaintiff relies on a drug's label accompanying the marketing of a drug to prove intent, "[t]he label must encourage, recommend, or promote infringement." Sanofi v. Watson Labs. Inc., 875 F.3d 636, 644 (Fed. Cir. 2017).

"For purposes of inducement, 'it is irrelevant that some users may ignore the warnings in the proposed label.'" Eli Lilly & Co. v. Teva Parenteral Medicines, Inc., 845 F.3d 1357, 1368 (Fed. Cir. 2017)(quoting AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1060 (Fed. Cir. 2010)). "The pertinent question is whether the proposed label instructs users to perform the patented method." AstraZeneca, 633 F.3d at 1060; see also Vita-Mix Corp. v. Basic Holding, Inc., 581 F.3d 1317, 1329 n. 2 (Fed. Cir. 2009) ("The question is not . . . whether a user following the instructions may end up using the device in an infringing way. Rather, it is whether [the] instructions teach an infringing use of the device such that we are willing to infer from those instructions an affirmative intent to infringe the patent.").

2. The Defendants' BLA Product Infringes the Asserted Claims of the Product Patent

Only one claim limitation is at issue as to the '865 Patent. The parties dispute whether Yesafili is an ophthalmic formulation containing an organic co-solvent comprising about 0.03% to about 0.1% polysorbate 20. Regeneron contends that the Defendants' BLA product satisfies this claim limitation because Yesafili contains [redacted] polysorbate 20 which increases the solubility of the aflibercept. The Defendants, however, assert that their BLA product does not infringe the Product Patent because polysorbate is not a co-solvent in Yesafili.

Regeneron must prove by a preponderance of the evidence that the BLA product satisfies every claim limitation. Roche Palo Alto LLC v. Apotex, Inc., 531 F.3d 1372, 1377 (Fed. Cir. 2008); Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1366 (Fed. Cir. 2003). As detailed below, the Court finds that Regeneron has satisfied this burden. Because Yesafili meets every limitation of the asserted claims, the Defendants infringe the Product Patent.

Both parties presented expert testimony on the topic of infringement of the Asserted Product Claims. Regeneron called Dr. Trout, who testified that the Defendants' Yesafili product infringes all of the Asserted Product Claims. Tr. 582:15-23 (Trout). The Defendants called Dr. MacMichael, who testified that,

in his opinion, the Asserted Product Claims are not infringed because the Defendants' Yesafili product does not contain an "organic co-solvent" under the Court's construction. Tr. 1375:9-15 (MacMichael). As explained below, the Court credits the testimony of Dr. Trout over the testimony of Dr. MacMichael on issues involving infringement of the asserted claims of the Product Patent.

a. Yesafili Satisfies All Undisputed Limitations of the Asserted Product Claims

The Defendants and Dr. MacMichael do not dispute that Yesafili meets every limitation of the Asserted Product Claims other than the "organic co-solvent" limitations. Dr. Trout's testimony that Yesafili meets all limitations of the Asserted Product Claims is therefore unrebutted as to all limitations other than "organic co-solvent."

i. Claim 1

Every Asserted Product Claim ultimately depends from claim 1. Dr. Trout testified that Yesafili meets each limitation of claim 1 of the Product Patent. Dr. Trout explained that [redacted] meets the requirement of claim 1 of "A vial comprising an

ophthalmic formulation suitable for intravitreal administration that comprises." Tr. 583:1-23 (Trout); PTX-1541.

Dr. Trout next testified that the requirement of "a vascular endothelial growth factor (VEGF) antagonist . . . wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4" [redacted]

Dr. Trout testified that the Defendants' Yesafili product meets the requirement of "a buffer" in claim 1. Tr. 627:1-21 (Trout). [redacted]

Dr. Trout further testified that the Defendants' Yesafili product meets the requirement of "a stabilizing agent" in claim 1.

Tr. 628:20-629:20 (Trout). [redacted]

[redacted]

Dr. Trout also addressed the limitation of claim 1 reciting "wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5°C. for two months as measured by size exclusion chromatography." Tr. 629:21-633:3 (Trout); PTX-66A; PTX-1820 at 9 (Table 2.3.P.8-6); PTX-1802 at 15-24. [redacted]

[redacted]

[redacted] [redacted] Dr. Trout thus concluded that the Defendants' Yesafili product meets this limitation of claim 1.

The Defendants and their non-infringement expert, Dr. MacMichael, offered no argument or evidence that their accused Yesafili product does not meet the foregoing limitations of claim 1. The Court credits Regeneron's unrebutted evidence, including the testimony of Dr. Trout, that the Defendants' Yesafili product meets each of the foregoing claim limitations.

Regarding the dependent claims, aside from the "organic co-solvent" limitation, the Defendants did not dispute at trial any limitations of any of the asserted dependent claims of the Product Patent. Regeneron, through its expert Dr. Trout, explained that the Defendants' Yesafili product meets each of these claim limitations, as summarized below. The Court credits Dr. Trout's unrebutted testimony.

ii. Claim 2

All of the Asserted Product Claims also depend from claim 2. Dr. Trout testified that the Defendants' Yesafili product meets the requirement of claim 2 that "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/mL." Tr. 587:6-588:5. Dr. Trout explained that Mylan's BLA submission states that its

product is formulated at a concentration of 40 mg/ml. Id.; PTX-1541 at 1. Dr. MacMichael did not dispute that the Defendants' product contains 40 mg/ml aflibercept. Tr. 1504:25-1505:2.

iii. Claim 7

Regarding claim 7, which recites "wherein said buffer comprises 5-25 mM buffer," Dr. Trout testified that the Defendants' Yesafili product contains a buffer as required by the asserted claims. Tr. 627:18-21. [redacted]

iv. Claim 9

Regarding claim 9, Dr. Trout testified that Defendants' Yesafili product meets the requirement that "wherein said buffer comprises a pH about 6.2-6.3." Tr. 627:22-628:19. [redacted]

v. Claims 10 and 11

Regarding claims 10 and 11, Dr. Trout testified that the Defendants' Yesafili product meets the limitations of these claims. Tr. 628:20-629:20. He testified that the trehalose stabilizing agent in Yesafili is a sugar, so Yesafili meets the requirement of claim 10 that "said stabilizing agent comprises a sugar." Id. He further testified that the trehalose stabilizing agent in Yesafili is among the sugars expressly listed in claim 11, so Yesafili meets the requirement of claim 11 that "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." Id.

vi. Claim 14

Regarding claim 14, Dr. Trout testified about the specific glycosylation sites on the aflibercept protein in the Defendants' product. As he explained, the aflibercept protein in the Defendants' product is glycosylated at the specific sites recited in claim 14. Tr. 585:18-586:8; PTX-3097 at 13 (the Defendants' proposed Yesafili label describing aflibercept as a "glycoprotein"). Thus, Yesafili meets the requirement of claim 14 that "wherein said VEGF antagonist fusion protein is glycosylated at asparagine residues corresponding to asparagine residues 62, 94, 149, 222 and 308 of SEQ ID NO: 4."

vii. Claim 15

Regarding claim 15, Dr. Trout testified that the Defendants' Yesafili product meets the additional limitation the of this claim. Tr. 639:2-640:8. [redacted]

viii. Claim 16

Regarding claim 16, Dr. Trout testified that [redacted]

[redacted] Dr. Trout thus concluded that Mylan's Yesafili product meets the claim element set forth in claim 16. Id.

ix. Claim 17

Regarding claim 17, Dr. Trout testified that [redacted]

[redacted] Dr. Trout thus concluded that Mylan's Yesafili product meets the claim element set forth in claim 17. Id.

b. Yesafili Satisfies the "Organic Co-solvent" Limitation of the Asserted Product Claims

Each Asserted Product Claim requires an "organic co-solvent" comprising "polysorbate"—either expressly or by virtue of its dependency on another patent claim. Claim 1 recites "an organic co-solvent"; claim 2 specifies that "said organic co-solvent comprises polysorbate"; claim 4 specifies that "said organic co-

solvent comprises about 0.03% to about 0.1% polysorbate 20"; and claim 5 specifies that "said organic co-solvent comprises 0.01% to 3% polysorbate 20."

The parties' only infringement dispute focuses on whether the polysorbate 20 undisputedly present in the Defendants' Yesafili product meets the claim requirement of an organic co-solvent comprising polysorbate 20. The Defendants argued at trial that, under the Court's construction, Yesafili's polysorbate 20 is not a co-solvent because it is not "added to the primary solvent"

(i.e., the water in Yesafili) "to increase the solubility of the solute, here a VEGF antagonist" (i.e., the aflibercept in Yesafili). Tr. 1375:23-1376:5 (MacMichael). By contrast, Regeneron maintained that Yesafili meets every limitation of the Asserted Product Claims, including the "organic co-solvent" limitation as that term was construed by the Court, by virtue of the polysorbate 20 in the Defendants' Yesafili product. Tr. 589:16-590:1 (Trout).

There was no dispute at trial that [redacted] Aggregation is the mechanism by which proteins like aflibercept come out of solution as a result of insolubility. Tr. 593:16-594:4, 598:13-10 (Trout); PTX-1556 at 3-4 (Wang). The Product Patent Inventors prevented the formation of insoluble particles in their intravitreal aflibercept formulations by including polysorbate 20. Tr. 483:4-10 (Furfine). Polysorbate achieved this objective by interacting with "hydrophobic patches" on the aflibercept molecules, thus preventing aggregation. Tr.

489:2-22 (Furfine), 595:5-596:14 (Trout). The term "hydrophobic" means "water-repelling" and refers to substances that are insoluble in water, like oil. Tr. 590:20-25 (Trout). "Hydrophilic" means "water-loving" and refers to substances that interact favorably with water. Id. Because polysorbate 20 has both hydrophobic and hydrophilic parts, PTX-1813A at 3; Tr. 590:12-591:6 (Trout), its hydrophobic part interacts favorably with hydrophobic regions of the protein and thereby prevents those hydrophobic patches from binding to other proteins and aggregating, Tr. 595:5-23 (Trout).

Preventing aflibercept from aggregating and coming out of solution is especially important in the context of intravitreal injections. Intravitreal injections use narrow needles, Tr. 472:21-473:8 (Trout); Tr. 1465:15-21 (MacMichael); Tr. 476:9-14 (Furfine), which lead to shear stress and enhanced risk of protein aggregation, Tr. 577:10-578:25 (Trout); Tr. 1465:19-25 (MacMichael). Forcing protein solutions through a narrow-bore needle creates shear stress, which can cause a protein to aggregate and come out of solution. Tr. 578:2-9 (Trout); Tr. 1465:15-25 (MacMichael); see also Tr. 476:2-24 (Furfine); Tr. 1680:6-11 (Graham). Polysorbate 20 protects against such stresses, preventing the aflibercept from aggregating and becoming insoluble. Tr. 1455:11-16, 1458:4-8, 1460:22-1461:13

(MacMichael). A protein coming out of solution can lead to several potential problems, including protein inactivation, inflammation, and even adverse immune responses. Tr. 578:25-579:10 (Trout). The critical question for formulation scientists, therefore, is not whether aflibercept stays in solution under non-stressed conditions, but rather whether it stays in solution under all of the temperature and pressure conditions attendant to the manufacture, storage, shipment, and use (including through narrow needles) of the product. Tr. 577:10-578:9, 580:16-22 (Trout).

The experts agreed that polysorbate 20 prevents the aggregation of aflibercept, Tr. 595:5-596:5, 596:22-597:2, 599:11-600:7 (Trout); Tr. 1407:15-20, 1408:13-18, 1460:17-1461:20 (MacMichael), and that preventing the aggregation of aflibercept keeps more aflibercept in solution, Tr. 600:12-20, 601:1-6, 601:14-602:15, 602:22-603:13 (Trout); Tr. 1412:11-14, 1458:4-14, 1459:2-1460:13, 1462:13-18 (MacMichael), i.e., increasing solubility of aflibercept as the Court's construction of "organic co-solvent" requires. [redacted]

[redacted]

[redacted]

The inventors used various labels to refer to polysorbate 20. In the Product Patent, in some internal documents, and in parts of their FDA submissions, they called it an "organic co-solvent." PTX-2, 2:39-42; Tr. 488:1-489:1 (Furfine); PTX-86 at 5 ("formulation development will require minimizing organic co-solvent (PEG and polysorbate)"); Tr. 1739:16-1740:22 (Graham); PTX-672 at 26 ("[A]ddition of an organic co-solvent (PEG3350, PEG300, or polysorbate 20) to the VEGF Trap drug substance significantly inhibited the degradation of 0.5 mg/ml VEGF Trap when agitated."). At times they referred to it as a stabilizer, stabilizing agent, or surfactant. Tr. 501:2-9 (Furfine). Regardless of its label, polysorbate 20 refers to a specific substance known to the POSA. Tr. 590:12-591:6 (Trout); PTX-1813A (Handbook of Pharmaceutical Excipients) at 3. And regardless of the particular English word used, polysorbate achieves the same function in aflibercept formulations—reducing aggregation that leads to aflibercept coming out of solution in the form of insoluble aggregations. Tr. 595:5-596:5, 596:22-597:2, 599:11-600:7 (Trout); Tr. 1407:15-20, 1408:13-18, 1460:17-1461:20 (MacMichael).

As relevant to the infringement inquiry, it was undisputed at trial that polysorbate 20 reduces formation of insoluble aggregates. Dr. Trout reviewed the scientific literature and explained how polysorbate 20 stabilizes proteins by preventing insoluble aggregates, thereby increasing the protein's solubility. The literature reflects the connection between reducing insoluble aggregates (which both parties agree polysorbate 20 does in aflibercept formulations, Tr. 595:5-596:5, 596:22-597:2, 599:11-600:7 (Trout); Tr. 1407:15-20, 1408:13-18, 1460:17-1461:20 (MacMichael)) and increasing solubility of a protein (the Court's construction of organic co-solvent, ECF No. 427 at 20; Tr. 600:12-20, 601:1-6, 601:14-602:15, 602:22-603:13 (Trout); Tr. 1412:11-14, 1458:4-14, 1459:2-1460:13, 1462:13-18 (MacMichael)). Wang 2005 elucidates how protein aggregation occurs: "[i]t is the patches of contiguous hydrophobic groups in the folding/unfolding intermediates that initiate the aggregation process." PTX-1556 at 3; Tr. 598:17-25 (Trout). Dr. Trout evaluated the three-dimensional structure of an aflibercept domain and confirmed that aflibercept has such hydrophobic patches that will be shielded by polysorbate, thereby increasing the solubility of aflibercept. Tr. 607:7-610:12; PTX-68A (showing hydrophobic regions in red). The Defendants offered no disagreement or contrary evidence. The Court credits Dr. Trout's unrebutted analysis.

The literature reflects the principle that as the hydrophobic patches of proteins associate, they begin to aggregate and become insoluble. "The initial protein aggregates are soluble but gradually become insoluble as they exceed certain size and solubility limits." PTX-1556 at 4; Tr. 599:1-7 (Trout). Polysorbate 20 prevents the formation of insoluble aggregates—protein out of solution. "To protect proteins from shaking/shearing-induced aggregation, surfactants are most commonly used," and these surfactants—including polysorbate, Tr. 601:14-25 (Trout), 1379:22-25 (MacMichael)— "inhibit protein aggregation by accumulating, competitively with proteins, at hydrophobic surfaces/interfaces and/or by binding directly to proteins." PTX-1556 at 20; Tr. 599:11-600:7. The hydrophobic/hydrophilic nature of polysorbate allows it to serve as a bridge between the hydrophobic patches of the protein and the aqueous (hydrophilic) solvent, thus inhibiting aggregation. PTX-1813A at 3; Tr. 590:12-591:6 (Trout). The Court finds that polysorbate 20's inhibition of the formation of insoluble aflibercept aggregates meets the Court's construction of "organic co-solvent."

Using a series of animations, Dr. Trout illustrated how polysorbate inhibits the formation of insoluble aggregates. Tr. 592:2-597:3. Dr. MacMichael did not dispute this understanding.

Tr. 1407:15-20, 1408:13-18, 1412:11-14, 1460:17-1461:20. Without polysorbate, aflibercept molecules aggregate and then fall out of solution as insoluble particles. Tr. 593:15-594:4, 599:1-7 (Trout); PTX-1556 at 4. In the presence of polysorbate 20, however, the hydrophobic end of the polysorbate 20 molecule interacts with the hydrophobic patches of aflibercept and "tends to hinder aggregation, and therefore, keep the molecules soluble." Tr. 595:5-596:5 (Trout). In other words, more aflibercept remains in solution with polysorbate 20 than without it; polysorbate 20 thus increases the solubility of aflibercept, consistent with the Court's claim construction. Id.; see Tr. 600:12-601:6 (Trout); Tr. 1461:22-1462:8 (MacMichael).

The literature confirms Dr. Trout's testimony and the link between reduced aggregation and increased solubility. The Randolph publication explained that interactions between surfactants and the hydrophobic patches on protein molecules lead to a "hydrophobicity reversal" that "effectively increases the solubility of the [surfactant-protein] complex":

> The hydrophobic portion of non-ionic surfactants can bind to hydrophobic patches on proteins. This naturally causes the surfactant to order itself so that more hydrophilic groups are solvent exposed, resulting in a "hydrophobicity reversal." This "hydrophobicity reversal" means that the protein-surfactant complex is more hydrophilic tha[n] either the surfactant or protein alone, and effectively increases the solubility of the complex.

PTX-1817 at 9-10 (emphasis added). Dr. Trout explained that Randolph "teach[es] exactly as I've been describing and exactly as the Wang article teaches," Tr. 601:14-20, and is "a reflection of the Court's construction of organic cosolvent. It increases the solubility of the complex."[6] Tr. 602:16-21. Neither the Defendants nor their experts offered a contrary interpretation of the literature, which reflects the understanding in the field that preventing aggregation is synonymous with increasing solubility. The Court credits Dr. Trout's unrebutted testimony.

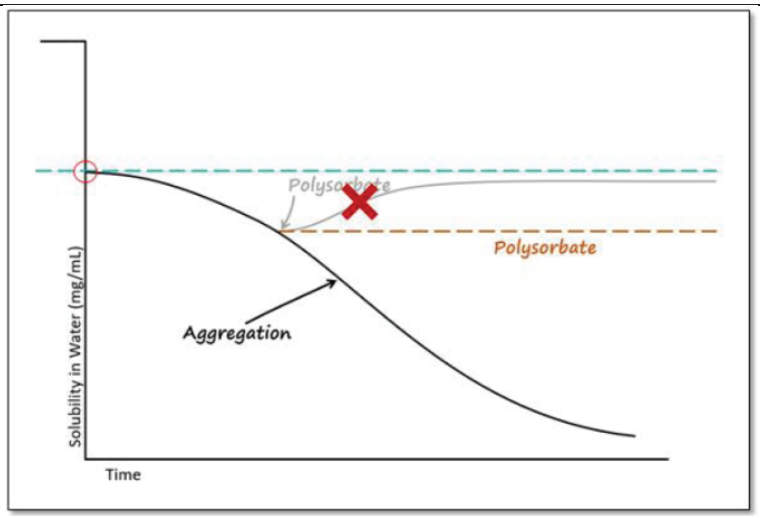
Randolph also addressed polysorbate 20 specifically, explaining that its "addition" "blocked the progression of aggregates from a relatively low molecular weight, soluble fraction to insoluble aggregates." PTX-1817 at 10. Dr. Trout confirmed Randolph's teaching that "just adding a very little bit of the polysorbate 20 starts to reduce the percentage of insoluble aggregates or increases the solubility." Tr. 604:12-606:8 (discussing PTX-1817 at 10, Fig. 4). In addition, Randolph demonstrates that surfactants like polysorbate 20 "increase[] the solubility of the complex" (here, aflibercept interacting with polysorbate) at low concentrations of polysorbate 20, thereby

[6] The "complex" referenced in Randolph corresponds to a "weak interaction" between the aflibercept protein and polysorbate—it is not a new molecule. Tr. 603:14-22 (Trout).

blocking the formation of insoluble aggregates. PTX-1817 at 9-10; Tr. 603:14-22 (Trout). The Court credits Dr. Trout's testimony and the teachings of Randolph, both of which demonstrate infringement.

The Defendants' argument that polysorbate 20 is not an organic co-solvent under the Court's construction and does not increase the solubility of aflibercept, see Tr. 1375:16-1376:5 (MacMichael), lacks support in the scientific literature, [redacted] and is contrary to the plain claim language reciting that the "organic co-solvent comprises . . . polysorbate 20." [redacted]

For example, Dr. MacMichael confirmed on cross-examination that polysorbate 20 increases the solubility of aflibercept. Dr. MacMichael presented the following demonstrative reflecting the effect of polysorbate 20 on protein solubility in water:



DDX-8.34. Discussing the graph, Dr. MacMichael agreed with Dr. Trout that "hydrophobic patches can interact and cause aggregation" of aflibercept "over time, if not protected" by polysorbate, Tr. 1458:6-8 (MacMichael). He also agreed that, if aflibercept aggregates "get large enough, they will fall out of solution," Tr. 1454:14-16, see also 1456:10-16, 1459:4-5 (MacMichael). This testimony contradicts the Defendants' argument that nothing can serve as an "organic co-solvent" for aflibercept in the claimed formulations because the aflibercept is fully soluble in water alone. Tr. 1452:11-16, 1405:16-1406:9 (MacMichael). As Dr. MacMichael agreed, "over time, if not protected" by polysorbate, the aflibercept will not remain in solution. Tr. 1458:6-8 (MacMichael). That is because the solubility of aflibercept in water is not an invariable constant,

but rather depends on external conditions such as time, pressure, and temperature. Tr. 1457:1-6 (MacMichael). As Dr. MacMichael admitted, a protein solution experiences changes in such conditions as it is handled and used—for example, "[a]s you push the liquid through" a narrow-gauge needle upon intravitreal administration, the protein molecule "[i]s experiencing shear." Tr. 1465:12-25 (MacMichael). Conditions such as "agitation-induced shear stresses" can increase aflibercept's "propensity for aggregation." Tr. 1466:19-1467:6 (MacMichael). And as Dr. MacMichael explained, the black curve in his graph shows the aflibercept "monomer in solution is going down over time as aggregates form." Tr. 1458:11-14. (A "monomer" is a "singular molecule of aflibercept," in contrast to aggregates of multiple aflibercept molecules. Tr. 1462:23-1463:8.)

Critically, Dr. MacMichael's figure shows that aflibercept's "Solubility in Water" with polysorbate in the formulation (the orange dashed line) is consistently higher than its solubility without polysorbate (the black curve). Dr. MacMichael confirmed that "[w]hat we're showing in this graphic is that," without polysorbate, "the monomer aggregates and falls out of solution. And when we add polysorbate, it would stop that aggregation." Tr. 1461:18-20 (emphasis added); see Tr. 1462:2-5 ("[W]ith polysorbate, you're going to prevent aggregation and the

[aflibercept] monomer from falling out of solution, either as soluble aggregates or insoluble aggregates."). Thus, as Dr. MacMichael agreed, "you have more monomer in solution with polysorbate than without," Tr. 1462:13-18—in other words, the polysorbate increases the solubility of aflibercept.

Dr. MacMichael and Dr. Trout thus did not substantively dispute the underlying scientific principles of how polysorbate 20 interacts with aflibercept to prevent aggregation and cause more aflibercept to remain in solution. Dr. MacMichael instead advanced two primary arguments in support of the Defendants' noninfringement position. First, he argued that the specification and claims of the Product Patent incorrectly describe polysorbate as a co-solvent. And second, he argued that that the Court's claim construction imposes an unstated requirement that is not met by the polysorbate in the Defendants' product. As explained below, the Court credits neither of these arguments.

First, by Dr. MacMichael's own admission, the claims and specification of the Product Patent expressly describe polysorbate as an organic co-solvent. For example, Dr. MacMichael acknowledged that asserted claim 4 recites "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." Tr. 1470:13-17 (MacMichael). In Dr. MacMichael's opinion, however, claim 4 is "inaccurate" and "doesn't make sense." Tr. 1471:4-18. He

testified that he "would have written" the claim differently. Tr. 1471:19-24 (MacMichael). In addition, he acknowledged that the Product Patent's specification repeatedly refers to polysorbate as an organic co-solvent, but he "disagree[d] with the wording" of the patent's specification. Tr. 1472:2-5, 1472:16-17 (MacMichael). He testified that the patent is "wrong" and "the way it's defining polysorbate as a cosolvent is incorrect." Tr. 1473:6-13 (MacMichael). In other words, Dr. MacMichael concedes that the Product Patent's specification expressly defines "organic co-solvent" to include polysorbate, and he further concedes that the claims likewise refer to polysorbate 20 as an "organic cosolvent" — he simply disagrees with the language chosen by the inventors to define and claim their patented invention. The Court declines to rewrite the Product Patent as Dr. MacMichael "[h]ypothetically . . . would have written" it if he were the inventor. Tr. 1471:19-24 (MacMichael). The specification and claims of the Product Patent are clear that polysorbate is an organic co-solvent, and the Court's construction reflects the language of the Product Patent. As explained above, there is no substantive dispute between Dr. Trout and Dr. MacMichael about how polysorbate 20 and aflibercept interact to prevent aflibercept from aggregating, thereby increasing the solubility of aflibercept under the Court's construction of "organic co-solvent."

Dr. MacMichael also argued that the Court's construction of "organic co-solvent" imposes an additional, unstated requirement—that the polysorbate must "dissolve" the aflibercept in order to qualify as an organic co-solvent. Tr. 1405:18-20, 1406:4-9, 1407:4-10 (MacMichael); see also Tr. 1577:21-22 (the Defendants' counsel arguing that "[t]he claim construction requires that a cosolvent has to actually help dissolve, get more things into solution"). To be clear, the Court's construction requires only that the organic co-solvent is "added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist." (ECF No. 427 at 20). It does not require that the organic co-solvent achieve the solubility increase in any particular way, and it specifies no requirement that the cosolvent "dissolve" the VEGF antagonist. Dr. MacMichael nonetheless argued that because aflibercept is "fully soluble and, therefore, would not need a cosolvent to further its solubility," polysorbate 20 cannot increase the solubility of aflibercept. Tr. 1452:11-16; see Tr. 1405:16-1406:9. As explained above, however, this argument is contradicted by Dr. MacMichael's own testimony that, "over time, if not protected" by polysorbate, aggregates of aflibercept "can fall out of solution," Tr. 1458:6-8, 1459:4-5. The additional requirement that Dr. MacMichael and the Defendants urge is not

part of the Court's construction, nor is it found anywhere in the Product Patent or the scientific literature.

As the parties' experts agreed, the notion of "dissolving" aflibercept has no scientific basis. The evidence was consistent that aflibercept is never "dissolved" upon formulation, because it is already in solution when formulated. Tr. 1469:5-9 (MacMichael) (acknowledging that from the time the molecule is synthesized by the cell through its "final formulation," the aflibercept molecule is "continuously in an aqueous environment" and "[i]s not in a solid format"); Tr. 576:5-8 (Trout) ("Typically, aggregates are irreversible. So once they form, they don't go backwards."); Tr. 1409:2-18 (MacMichael) (agreeing with Dr. Trout); see also Tr. 505:4-12, 531:8-11, 561:15-562:8 (Furfine); Tr. 1677:4-7 (Graham). Rather, the evidence showed that a cosolvent may increase the solubility of aflibercept by preventing it from becoming insoluble. As described above, "with polysorbate, you're going to prevent aggregation and the [aflibercept] monomer from falling out of solution" and forming "insoluble aggregates." Tr. 1462:2-5 (MacMichael); see also Tr. 562:2-8 (Furfine). In this way, polysorbate 20 serves to "increase the solubility" of aflibercept.

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MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

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MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

[redacted]

[redacted] Even if the Court did not consider this testimony, however, that would not change the Court's rulings in favor of Regeneron as to the Product Patent.

Dr. MacMichael's only response to [redacted]

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MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

In sum, having considered the evidence and testimony at trial regarding whether Yesafili contains an "organic co-solvent [that] comprises . . . polysorbate 20" under the Court's construction, the Court concludes that the [redacted] polysorbate 20 in the Defendants' Yesafili product meets the requirements of the asserted claims of an organic co-solvent that comprises polysorbate 20. In doing so, the Court finds Dr. Trout's testimony to be more credible than Dr. MacMichael's. [redacted] And Dr. MacMichael misapplied the Court's claim construction in arguing that [redacted]

[redacted] the Court's construction requires only that the organic co-solvent is "added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist" — not that the organic co-solvent achieve the increased solubility in any particular way. (ECF No. 427 at 20).

c. Conclusion

As explained, the only infringement dispute between the parties regarding the Product Patent is whether the polysorbate 20 in the Defendants' Yesafili product meets the "organic co-solvent" claim limitation under the Court's construction of that term. In other words, the dispute centers on whether the polysorbate 20 in the Defendants' Yesafili product "is added to the primary solvent [i.e., the water in the Defendants' Yesafili product] to increase the solubility of" the aflibercept in the Defendants' Yesafili product. (ECF No. 427 at 20).

The Randolph publication explained that interactions between surfactants like polysorbate 20 and the hydrophobic patches on protein molecules lead to a "hydrophobicity reversal" that "effectively increases the solubility of the [surfactant-protein] complex." PTX-1817 at 9-10. And Wang 2005 elucidates how protein aggregation occurs: "[i]t is the patches of contiguous hydrophobic groups in the folding/unfolding intermediates that initiate the

aggregation process." PTX-1556 at 3; Tr. 598:17-25 (Trout). Randolph also addressed polysorbate 20 specifically, explaining that its "addition" "blocked the progression of aggregates from a relatively low molecular weight, soluble fraction to insoluble aggregates." PTX-1817 at 10.

Notably, the Defendants' infringement expert, Dr. MacMichael, did not respond to the pertinent teachings of Wang 2005 and Randolph, and did not dispute Dr. Trout's analysis of how polysorbate 20 interacts with aflibercept. Dr. Trout's testimony thus stands unrebutted and compels a judgment of infringement. See Raytheon Techs. Corp. v. Gen. Elec. Co., 993 F.3d 1374, 1382 (Fed. Cir. 2021) ("unrebutted evidence" on issue was "conclusive"); Imperium IP Holdings v. Samsung Elecs. Co., 757 F. App'x 974, 978-79 (Fed. Cir. 2019) (no reasonable basis to reject opinion of expert whose "testimony was not contradicted" or impeached).

While Dr. MacMichael and Dr. Trout did not substantively dispute the underlying principles for how polysorbate 20 interacts with aflibercept, Dr. MacMichael asserted that the Court's claim construction imposes several requirements that are found nowhere in the Product Patent or the literature. He argued that because aflibercept is "fully soluble and, therefore, would not need a cosolvent to further its solubility," polysorbate 20 cannot

increase the solubility of aflibercept. Tr. 1452:11-16; see Tr. 1405:16-1406:9. But the Court's construction does not require the co-solvent to "dissolve" aflibercept. Tr. 1405:18-24 (MacMichael). Under the Defendants' interpretation of the construction, Dr. MacMichael could identify *nothing* that could serve as a co-solvent for aflibercept in the claims, confirming that the Defendants improperly seek to impose a requirement that cannot be satisfied. See Lisle Corp. v. A.J. Mfg. Co., 398 F.3d 1306, 1314 (Fed. Cir. 2005) (rejecting "hyper-technical reading" requiring "tool disclosed by the patent" to perform function it was "incapable" of performing); Kenall Mfg. Co. v. H.E. Williams, Inc., 2013 WL 427119, at *2 (N.D. Ill. Feb. 1, 2013) ("[R]eadings of patents are to be avoided where they would arrive at an absurd result rather than achieve a common sense meaning."). The Court's construction requires only that the organic co-solvent is "added to the primary solvent to increase the solubility of the solute, here a VEGF antagonist." (ECF No. 427 at 20). It does not require that the organic co-solvent achieve the increase in solubility in any particular way.

The evidence was unequivocal that aflibercept is never "dissolved" upon formulation, because it is already in solution when formulated. Tr. 505:4-12, 531:8-11, 561:15-562:8 (Furfine); Tr. 1677:4-7 (Graham); Tr. 576:5-8 (Trout) ("Typically, aggregates

are irreversible. So once they form, they don't go backwards."); Tr. 1469:5-9 (MacMichael) ("From the time that the molecule is synthesized by the cell it's in an aqueous environment. . . It's not in a solid format."), 1409:2-18 (MacMichael) (agreeing with Dr. Trout). Rather, as described above, polysorbate 20 serves to "protect against degradation and precipitation and falling out of solution." Tr. 562:2-8 (Furfine). Although Dr. MacMichael asserted that aflibercept is "fully soluble" without polysorbate 20, Tr. 1403:4-7, he admitted that "hydrophobic patches can interact and cause aggregation" of aflibercept "over time, if not protected" by polysorbate, Tr. 1458:6-8, and that if aflibercept aggregates "get large enough, they will fall out of solution," Tr. 1454:13-15; see also Tr. 1456:10-16, Tr. 1459:4-5. Critically, Dr. MacMichael agreed that the figure he discussed on direct examination showed that "you have more monomer in solution with polysorbate than without," Tr. 1462:13-18—in other words, the polysorbate increases the solubility of aflibercept. By protecting against such aggregation and precipitation, polysorbate 20 "increase[s] the solubility" of aflibercept, and thus is an "organic co-solvent" under the Court's construction and the plain terms of the patent.

The Defendants also argue that [redacted]

[redacted] it cannot meet the "organic co-solvent compris[ing] . . . polysorbate 20" limitation. This argument epitomizes form over substance. The Product Patent describes polysorbate 20 as an organic co-solvent. E.g., PTX-2, 2:39-40; Tr. 1473:6-13 (MacMichael) (agreeing the patent "[is] defining polysorbate as a cosolvent" but contending the patent "is incorrect"); Tr. 2098:19-22 (Trout). It is well-established that chemicals may appropriately be described using different labels, which is of little moment where, as here, the patent specification and claims identify polysorbate 20 expressly as an organic co-solvent. PTX-2, claim 4, 2:39-42; see Celgene Corp. v. Hetero Labs Ltd., 2020 WL 3249117, at *12 (D.N.J. June 16, 2020) ("[N]othing in the specification or the prosecution history supports . . . that the 'lubricant' has to be a substance that is 'distinct from' a binder or filler."); Roche Palo Alto LLC v. Lupin Pharm., Inc., 2012 WL 983697, at *18 (D.N.J. Mar. 21, 2012) ("[I]ngredients can overlap by serving multiple functions within a given formulation."). By contrast, the patent identifies substances other than polysorbate as stabilizing agents. PTX-2, 2:44-45. The Defendants cannot avoid infringement merely by [redacted]

Dr. MacMichael acknowledges the patent's unambiguous description of polysorbate 20 as a co-solvent; he just thinks the patent "is wrong." Tr. 1470:21-23. But disagreement with a patent is not a defense to patent infringement. Patent infringement "is a strict liability offense" and judgment must follow "regardless of the intent, culpability or motivation of the infringer." Jurgens v. CBK, Ltd., 80 F.3d 1566, 1570 n.2 (Fed. Cir. 1996).

[redacted]—and Regeneron referred to polysorbate 20 as an organic co-solvent repeatedly, including in the Product Patent and the Eylea BLA. PTX-2, 2:39-42; Tr. 488:1-489:1 (Furfine); PTX-86 at 5 ("formulation development will require minimizing organic co-solvent (PEG and polysorbate)"); Tr. 1739:16-1740:22 (Graham); PTX-672 at 26 ("[A]ddition of an organic co-solvent (PEG3350, PEG300, or polysorbate 20) to the VEGF Trap drug substance significantly inhibited the degradation of 0.5 mg/ml VEGF Trap when agitated.").

The Court declines to rewrite the Product Patent as Dr. MacMichael "[h]ypothetically . . . would have written" it if he

were the inventor. Tr. 1471:19-24 (MacMichael). The specification and claims of the Product Patent are clear that polysorbate is an organic co-solvent, and the Court's construction reflects the language of the Product Patent. Thus, the Court concludes that polysorbate 20 meets the "organic co-solvent" claim element [redacted]

For these reasons, the Court concludes that Regeneron has demonstrated by a preponderance of the evidence that the Defendants' BLA Product infringes the asserted claims of the Product Patent.

3. The Defendants' BLA Product Induces Infringement of the Treatment Patents

The parties next dispute whether the Defendants' BLA product and proposed instructions and label will induce infringement of

the Treatment Claims, claims 11 and 19 of the '601 Patent and claims 6 and 25 of the '572 Patent. The Treatment Claims relate to the treatment of angiogenic eye disorders using Regeneron's dosing regimen: a period of every-four-week dosing of aflibercept followed by at least one eight-week dose of aflibercept. These claims fall into three categories: (1) claims involving methods of treating DME by administering aflibercept in a series of five monthly loading doses followed by one or more subsequent doses spaced eight weeks apart - claim 11 of the '601 Patent and claim 25 of the '572 Patent (the "DME Claims"); (2) a claim involving a method of treating DR by administering aflibercept in a series of five monthly loading doses followed by one or more subsequent doses spaced eight weeks apart – claim 19 of the '601 Patent (the "DR Claim"); and (3) a claim involving a method of treating an angiogenic eye disorder by administering aflibercept in an isotonic solution in a series of every-four-week loading doses followed by one or more subsequent doses spaced eight weeks apart - claim 6 of the '572 Patent (the "Angiogenic Eye Disorder Claim").

Regeneron asserts that the Defendants' prescribing information for Yesafili will induce infringement of the Treatment Claims because its label and marketing recommend that physicians administer the BLA product in an infringing manner. The Defendants, on the other hand, argue that Regeneron has failed to

demonstrate that physicians will use Yesafili in an infringing way if commercialized or that the Defendants intended to induce infringement.

As detailed below, the Court finds that (1) if the Defendants market Yesafili with its proposed label, some physicians will follow the recommendations in that label and will thereby perform acts that directly infringe the Treatment Claims, and (2) the Defendants' proposed label for Yesafili encourages, recommends, and promotes administration of Yesafili in an infringing manner. Accordingly, the Court finds that the Defendants will induce infringement of the Treatment Claims if they market Yesafili.

a. Physicians Will Use the Defendants' BLA product in an Infringing Manner

The evidence at trial demonstrated that if the Defendants market Yesafili with its proposed label, some physicians will follow its recommendations and treat patients in a manner that directly infringe the Treatment Claims. Regeneron presented expert testimony on the topic of infringement of the Treatment Claims, through its clinical expert Dr. Karl Csaky, whom the Court accepted as an expert in ophthalmology with a specialty in angiogenic retinal diseases and their treatment in view of his extensive qualifications, detailed above. The Defendants did not offer opposing expert testimony.

Dr. Csaky testified that the Defendants induced infringement of each Asserted Treatment Claim by the express instructions in the proposed label for Yesafili. See Tr. 345:10-23, 360:17-361:6, 371:23-372:8, 373:17-20, 381:21-382:9, 388:21-389:5 (Csaky); see also PTX-3097 (the Defendants' August 2022 label); PTX-3338 (the Defendants' March 2023 label, which they produced after expert discovery, and which is substantively identical to the August 2022 label, Tr. 311:4-312:9 (Csaky)). No witness testified to the contrary. As Dr. Csaky explained, he and other ophthalmologists read labels, and the label for a drug "gives us a starting point for how do we utilize the drug." Tr. 331:18-333:7 (Csaky). The Defendants' clinical expert Dr. Jay Stewart admitted on cross-examination that he has reviewed labels for Eylea in his clinical practice. Tr. 1350:6-10 (Stewart).

Dr. Csaky also testified that if the Defendants market Yesafili accompanied by their proposed label, at least some doctors will follow the label instructions and therefore perform the methods of the Treatment Claims in some patients. Tr. 367:4-371:22 & 379:17-381:20 (Csaky) (DME Claims); Tr. 386:10-388:20 (Csaky) (DR Claim); Tr. 331:3-345:9 & 355:5-360:16 (Csaky) (Angiogenic Eye Disorder Claim). Dr. Csaky based those opinions on his experience, Tr. 304:13-25, 307:16-309:1, 331:18-333:7, 334:12-337:4, 344:19-345:9, 356:7-358:9, 360:3-16, 367:4-371:22,

379:17-381:20, 386:10-388:20 (Csaky), his discussions with fellow ophthalmologists, Tr. 304:13-25, 307:16-309:1, 334:12-335:6, 337:5-25, 344:19-345:9, 356:7-358:4, 358:21-359:7, 360:3-16, 367:4-371:22, 379:17-381:20, 387:1-388:20 (Csaky), the sworn testimony of other ophthalmologists, Tr. 339:2-341:16, 344:19-345:9, 358:10-20, 360:3-16 (Csaky), and peer-reviewed literature, Tr. 341:19-345:9 (Csaky); see also PTX-586. He also grounded his opinions in the fact that ophthalmologists, including Dr. Csaky himself, have performed these methods with Eylea, which has a substantively identical label. Tr. 333:17-337:25, 339:2-344:18, 355:11-359:7, 359:20-360:16, 369:4-371:6, 380:18-381:20, 386:10-388:20 (Csaky).

At trial, the Defendants objected to Dr. Csaky's reliance on the written testimony of Dr. Diana Do that Regeneron submitted in an IPR proceeding, as informing his understanding that ophthalmologists make use of the dosing regimens set forth in the Eylea label in various contexts. Tr. 433:17-34 (Csaky). Regeneron did not and does not request admission of the underlying Declaration itself, but Dr. Csaky was permitted to reference it in explaining how he formed his opinions. Tr. 338:14-18 (Csaky). As a qualified expert, Dr. Csaky was permitted to rely on his understanding of practices in the field as informed by his understandings from other ophthalmologists. Fed. R. Evid. 703.

Just as he could consider views as expressed in written publications or in oral conversations, there is no reason he could not take into account the views of another expert as set forth in a written declaration made under oath. Dr. Csaky testified that he knows Dr. Do, has co-authored a paper with her, and finds her trustworthy. Tr. 339:12-340:21, 433:5-15, 1833:13-21, 2003:20-2005:6 (Csaky); PTX-1027. One of the Defendants' experts, Dr. Albini, agreed that she is well-regarded. Tr. 884:14-16 (Albini). Also, as Dr. Csaky explained in his testimony, physicians frequently rely on the opinions of physicians who are paid by industry leaders for their work, and he himself has done so in the context of his own research. Tr. 432:11-15 (Csaky). The Court will consider Dr. Csaky's testimony about the Do declaration, but not the declaration itself, in its infringement analysis. Even if the Court did not consider Dr. Csaky's testimony relying on the Do declaration, however, it would not change the Court's infringement analysis.

As Mylan's Rule 30(b)(6) corporate representative and Director of Core Regulatory Labeling Strategy, Vanessa Smith, testified, "we based our labeling [for Yesafili] off of the reference product labeling [for Eylea]," ECF No. 538-3 at 48:16-17; the Yesafili label contains "the same indications that are listed on the current Eylea label" and instructs treatment using

"the same dosage regimens that are reflected on the current Eylea label," ECF No. 538-3 at 31:17-32:22; and the purpose for including such statements in the label was to "provide the information pertaining to how the product should be dosed for the defined indications . . . and how that product should be administered . . . for each particular indication," ECF No. 538-3 at 32:8-17. Copying the label for Eylea allowed the Defendants to take advantage of an abbreviated path to FDA approval by using dosing regimens that Regeneron developed and tested at great expense with clinical trials, the cost of which "can easily run in the hundreds of millions of dollars." Tr. 1590:2-3 (Chu).

b. The Defendants' BLA product Label Recommends Infringing Uses

Further, the Defendants' proposed label for Yesafili encourages, recommends, and promotes administration of Yesafili in a manner that meets every limitation of each of the Treatment Claims.

i. The DME Claims (Claim 11 of the '601 Patent and Claim 25 of the '572 Patent)

With regard to the DME Claims, the Defendants' Yesafili label recommends, encourages and promotes clinicians to use Yesafili to treat "Diabetic Macular Edema (DME)," consistent with claim 10 of

the '601 patent and claim 15 of the '572 patent, from which the asserted claims depend.

The Yesafili label recommends only one dosing regimen for the treatment of DME. Tr. 347:4-25, 349:2-17 (Csaky); PTX-3097 at 1-2; see also Tr. 303:19-304:1, 313:18-22 (Csaky) (Eylea and Yesafili labels recommend the same thing). Specifically, the label recommends ophthalmologists treat DME by administering 2 mg Yesafili "by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)." This recommended regimen meets every limitation of claim 11 of the '601 patent and claim 25 of the '572 patent, as Dr. Csaky testified, and as set forth in more detail below. Tr. 361:12-367:3, 374:11-379:16 (Csaky).

1) Claim 25 of the '572 Patent

The Defendants' proposed label for Yesafili recommends that doctors perform every step of the method of claim 25 as to which the Court has afforded patentable weight, including those limitations incorporated by virtue of claim 25's dependency on claim 15. Specifically, the Defendants' proposed label for Yesafili recommends that doctors perform:

- "A method for treating diabetic macular edema in a patient in need thereof" (see PTX-3097 at 2; see also PTX-3097 at 1; Tr. 362:11-24, 375:8-376:13 (Csaky));
- "sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept . . . wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose" . . . "wherein four secondary doses are administered to the patient" (see PTX-3097 at 2; see also PTX-3097 at 1 ("2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections"); Tr. 362:25-365:7, 376:14-378:11 (Csaky));
- "and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose" (see PTX-3097 at 2; see also PTX-3097 at 1; Tr. 365:8-366:12, 378:12-379:2 (Csaky)).

The evidence also demonstrates that if the Defendants market Yesafili, some physicians will perform the steps recommended in its proposed label and thereby directly infringe claim 25 of the

'572 patent. As described above, Dr. Csaky testified that some physicians would follow the instructions in Yesafili's label based on, among other things, his own experience and discussions with fellow ophthalmologists. Tr. 367:4-371:22 (Csaky discussing claim 25); ¶¶ 162-63 (Csaky testimony regarding physicians reviewing labels and performing methods described in Yesafili and Eylea labels); Tr. 369:3-370:1 (Csaky testimony that Eylea and Yesafili labels both recommend infringement of claim 25).

For example, Dr. Csaky testified that based on "the way that doctors currently use" Eylea, "there will be some doctors who will perform these methods" as recommended in Yesafili's label, and that he personally has used those methods to treat DME, as claim 25 requires. Tr. 355:5-356:21 (Csaky). Dr. Csaky elaborated that "it's very common to say we're going to try five injections at the very beginning, especially for someone with diabetic macular edema; and then, of course, if they respond well, then you want to start extending them to a longer period, like eight weeks." Tr. 357:4-9 (Csaky).

Accordingly, the Court finds that if the Defendants market Yesafili, the Defendants will induce infringement of claim 25 of the '572 patent.

2) Claim 11 of the '601 Patent

The Defendants' proposed label for Yesafili recommends that doctors perform every step of the method of claim 11 having patentable weight, including those limitations incorporated by virtue of claim 11's dependency on claim 10. Specifically, the Defendants' proposed label for Yesafili recommends that doctors perform:

- "A method for treating diabetic macular edema in a patient in need thereof" (see PTX-3097 at 2; see also PTX-3097 at 1; Tr. 362:11-24, 375:8-376:13 (Csaky));
- "comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections" (see PTX-3097 at 2; see also PTX-3097 at 1 ("2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections"); Tr. 362:25-365:7, 376:14-378:11 (Csaky));
- "followed by 2 mg approximately once every 8 weeks or once every 2 months" (see PTX-3097 at 2; see also PTX-3097 at 1; Tr. 365:8-366:12, 378:12-379:2 (Csaky));
- "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly" (see

PTX-3097 at 2; see also PTX-3097 at 1; Tr. 377:16-378:11 (Csaky)).

The evidence also demonstrates that if the Defendants market Yesafili, some physicians will perform the steps recommended in its proposed label and thereby directly infringe claim 11 of the '601 patent. As described above, Dr. Csaky testified that some physicians would follow the instructions in Yesafili's label based on, among other things, his own experience and discussions with fellow ophthalmologists. Tr. 379:18-381:20 (Csaky); supra ¶¶ 162-63. In addition to the testimony Dr. Csaky provided in the context of claim 25, supra ¶ 169—all of which is relevant to claim 11—Dr. Csaky specifically testified that doctors will also perform claim 11's additional limitation—administering aflibercept once every four weeks for the first five injections, "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly" — which is consistent with his own practice and the practice of other ophthalmologists with whom he has spoken. Tr. 380:5-381:9 (Csaky) ("Yes. I would say that we often do this approximately every 28 days.").

Accordingly, the Court finds that if the Defendants market Yesafili, the Defendants will induce infringement of claim 11 of the '601 patent.

ii. The DR Claim (Claim 19 of the '601 Patent)

The Defendants' proposed label for Yesafili recommends that doctors perform every step of the method of claim 19 of the '601 patent having patentable weight, including those limitations incorporated by virtue of claim 19's dependency on claim 18. Specifically, the Defendants' proposed label for Yesafili recommends that doctors perform:

- "A method for treating diabetic retinopathy in a patient in need thereof" (see PTX-3097 at 1, 3; Tr. 383:6-25 (Csaky));
- "comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections" (see PTX-3097 at 3; see also PTX-3097 at 1; Tr. 384:1-385:4 (Csaky));
- "followed by 2 mg approximately once every 8 weeks or 2 months" (see PTX-3097 at 3; see also PTX-3097 at 1; Tr. 385:5-24 (Csaky));
- "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly" (see PTX-3097 at 3; see also PTX-3097 at 1; Tr. 384:1-385:4 (Csaky)).

The evidence also demonstrates that if the Defendants market Yesafili, some physicians will perform the steps recommended in its proposed label and thereby directly infringe claim 19 of the '601 patent. Dr. Csaky testified that he has personally performed and that others have performed the method of claim 19 to treat DR using Eylea, and that in his opinion, some doctors will follow Yesafili's label for the treatment of patients with DR. Tr. 386:11-388:20 (Csaky). Dr. Csaky elaborated that "there's more and more interest in using this approach," and that he has talked with other physicians "about the utility of this approach in treating these types of patients, and they claim that they are using this approach" especially "where the alternative is laser photocoagulation. Tr. 387:1-10 (Csaky); see also Tr. 357:10-358:9 (Csaky).

Accordingly, the Court finds that if the Defendants market Yesafili, the Defendants will induce infringement of claim 19 of the '601 patent.

iii. The Angiogenic Eye Disorder Claim (Claim 6 of the '572 Patent)

The Defendants' proposed label for Yesafili recommends that doctors perform every step of the method of claim 6 of the '572 patent having patentable weight, including those limitations incorporated by virtue of claim 6's dependency on claims 1, 2, and

3. Specifically, the Defendants' proposed label for Yesafili recommends that doctors perform the following steps for the treatment of each of AMD, DME, and DR.

- "A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept" (AMD, DME, and DR: see PTX-3097 at 2-3; id. at 1; Tr. 316:22-318:10, 346:3-347:3 (Csaky))
- "followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose . . . wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose" (AMD: see PTX-3097 at 2; id. at 1; Tr. 318:11-323:21 (Csaky); DME and DR: PTX-3097 at 2-3; id. at 1; Tr. 347:4-352:8 (Csaky));
- "followed by one or more tertiary doses of 2 mg of aflibercept . . . wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose" (AMD: PTX-3097 at 2; id. at 1;

Tr. 323:22-325:9 (Csaky); DME and DR: PTX-3097 at 2-3; id. at 1; Tr. 352:9-353:20 (Csaky));

- "wherein the aflibercept is formulated as an isotonic solution (AMD, DME and DR: PTX-3097 at 13; PTX-1800 at 2; PTX-1820 at 14; Tr. 642:5-15, 640:9-641:23, 640:9-642:22 (Trout)).

With respect to the final limitation of claim 6, [redacted] Tr. 1168:25-1169:2 (Rabinow) (agreeing "isotonic and iso-osmolar have roughly the same meaning"); see also Tr. 526:22-527:1 (Furfine).

The evidence also demonstrates that if the Defendants market Yesafili, doctors will follow the recommended dosing regimens for AMD, DME, and DR and will therefore perform acts of direct infringement. As he testified with regard to the Yesafili label's instructions for treating DME and DR, Dr. Csaky testified that at least some doctors would follow the label's instructions for treating wet AMD, and in fact that those instructions reflect "a very common approach" that he and other doctors use with patients. Tr. 333:8-337:25 (Csaky). Dr. Csaky also properly relied on the sworn declaration of a renowned ophthalmologist, Dr. Diana Do, who testified that she and other physicians "typically and frequently treat wet AMD" as well as "other diseases like diabetic macular edema, DME, or diabetic retinopathy" by using the method of claim 6 of the '572 Patent. Tr. 339:2-341:16 (Csaky); see PTX-1527 (Decl. of Diana Do).

iv. Additional Evidence of Infringement

Even were the specific dosing regimens discussed above not included in Yesafili's label, other statements in the Defendants' proposed Yesafili label are sufficient to induce infringement because those statements convey to ophthalmologists that Yesafili should be used identically to the way in which some ophthalmologists already administer Eylea. See Tr. 331:3-345:9,

355:5-361:7, 367:4-371:22, 379:17-381:20, 386:10-388:20, 393:10-396:1 (Csaky).

First, Dr. Csaky considered language that the Defendants included in their Yesafili label, stating that Yesafili is "highly similar" to Eylea, that "there are no clinically meaningful differences between" Yesafili and Eylea, and that Yesafili "can be expected to produce the same clinical result as [Eylea] in any given patient." PTX-3097 at 1. This language was optional, not required by the FDA, as Mylan's Rule 30(b)(6) corporate representative and Director of Core Regulatory Labeling Strategy, Vanessa Smith, acknowledged. (ECF No. 538-3 (Smith) at 110:08-112:09, 114:05-115:13, 117:12-118:10). Dr. Csaky testified — unrebutted — that this language alone conveys to clinicians that "the two drugs are the same" and that they "can use Yesafili in the exact same way [they] can use Eylea." Tr. 394:20-396:1 (Csaky). Accordingly, the Court concludes that this language alone, without regard to any other language in the label, demonstrates the Defendants' inducement of infringement.

Second, Dr. Csaky considered language that the Defendants included in their Yesafili label, stating that Yesafili is "interchangeable" with Eylea. PTX-3097 at 1. Again, this language was optional, not required by the FDA, as Mylan's Rule 30(b)(6) corporate representative acknowledged. (ECF No. 538-3 (Smith) at

110:08-112:09, 114:05-115:13, 117:12-118:09). Dr. Csaky testified — unrebutted — that this language would convey to clinicians that "the two drugs are the same" and that they "can essentially exchange and use Yesafili in the exact same fashion that [they are] using Eylea in the clinic." Tr. 394:1-19 (Csaky).

Third, Dr. Csaky considered statements the Defendants made in a presentation delivered by their consultant, Dr. Susan Bressler, at the 2022 meeting of the American Academy of Ophthalmology ("AAO"). See PTX-331. The AAO meeting is the "largest ophthalmology meeting" in the country that "all general ophthalmologists, retina specialists will attend" and that "is the one place where you can disseminate information and share the results of data with the community." Tr. 390:5-17 (Csaky). In their presentation, the Defendants stated that they had performed a Phase 3 trial in which Yesafili was administered in a baseline dosing regimen within the scope of the DME Claims and the Angiogenic Eye Disorder Claim, see PTX-331 at 5-6, and announced that the study had "demonstrated therapeutic equivalence of [Yesafili] and [Eylea] in the treatment of diabetic macular edema (DME)," that Yesafili "was safe and well tolerated, with a similar safety and immunogenicity profile to . . . Eylea," and that "[f]ollowing regulatory approval, [Yesafili] is expected to be a new treatment option for patients with DME," id. at 12. Dr. Csaky

testified — unrebutted — that ophthalmologists would understand such statements to convey that they could "use Yesafili essentially in an identical way that [they are] using Eylea in the treatment of DME." Tr. 393:10-21 (Csaky). This evidence supports a finding that the Defendants actively encourage infringement of the Treatment Claims as to DME.

The Defendants offered no expert testimony to rebut Dr. Csaky's conclusions on infringement. The Court credits Regeneron's unrebutted evidence of infringement, including the testimony of Dr. Csaky, that if the Defendants market Yesafili, the Defendants will induce infringement of each of the Treatment Claims.

c. Conclusion

The Defendants induce infringement of the Treatment Patents because they propose to sell Yesafili with prescribing information that will explicitly encourage, recommend, and promote its administration in a manner that would infringe the Treatment Claims, and it is undisputed that some doctors will follow the label and use Yesafili to treat patients in an infringing way. Federal Circuit "precedent has consistently held that, when a product is sold with an infringing label or an infringing instruction manual, such a label is evidence of intent to induce

infringement." GlaxoSmithKline, 7 F.4th at 1334; see also Sanofi, 875 F.3d at 646; Eli Lilly, 845 F.3d at 1368; AstraZeneca, 633 F.3d at 1059.

To the extent that the Defendants argue that some doctors will ignore the label directions and engage in noninfringing uses of Yesafili, see Tr. 713:16-22, 715:10-18, the Federal Circuit has rejected this argument. In AstraZeneca v. Apotex, the Federal Circuit acknowledged that "where a product has substantial noninfringing uses," intent to induce infringement could not be inferred from a defendant's mere knowledge that its product might be put to infringing use, but clarified that "liability for active inducement may be found where evidence goes beyond a product's characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement." 633 F.3d at 1059. Here, the Defendants' label instructions meet this standard and "encourage, recommend, or promote" infringing conduct, particularly given the Defendants' continued pursuit of FDA approval of those instructions despite repeated notice of Regeneron's infringement claims. See, e.g., id. at 1060; Sanofi, 875 F.3d at 646 (rejecting argument that because product "has substantial noninfringing uses not forbidden by the proposed labels . . . the district court could not permissibly find intent to encourage an infringing use" and

concluding "there is no legal or logical basis for the suggested limitation on inducement"); GlaxoSmithKline, 7 F.4th at 1334 ("Our precedent has consistently held that, when a product is sold with an infringing label or an infringing instruction manual, such a label is evidence of intent to induce infringement.").

To the extent that the Defendants argue that the Yesafili label discusses noninfringing uses, including potential alternative regimens, the Federal Circuit also has rejected that argument. In GlaxoSmithKline, the accused infringer contended its label language about treating two categories of patients, when arguably the treatment of only one category fell within the scope of the claim, "preclude[d] inducement since this may encourage both infringing and noninfringing uses." Id. at 1329. The court rejected the argument that the "label's recommended use on both types of patients somehow obviates infringement." Id. at 1330. In Vanda, the court similarly rejected a noninfringement argument based on a label's target dose range allowing for the use of both infringing and noninfringing doses. 887 F.3d at 1132. The court explained that "[e]ven if not every practitioner will prescribe an infringing dose, that the target dose range 'instructs users to perform the patented method' is sufficient to 'provide evidence of . . . affirmative intent to induce infringement.'" Id. (quoting AstraZeneca, 633 F.3d at 1060).

The Defendants also induce infringement of the Treatment Patents because their marketing has instructed and will instruct health care providers to administer Yesafili in the same infringing manner they have administered Eylea for many years, and it is undisputed that some doctors will follow those directions and use Yesafili to treat patients in an infringing way. As the Federal Circuit stated in AstraZeneca, "liability for active inducement may be found where evidence goes beyond a product's characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement." 633 F.3d at 1059.

Here, such statements or actions included the Defendants' statements in their label that Yesafili is "highly similar" to Eylea, that "there are no clinically meaningful differences between" Yesafili and Eylea, that Yesafili "can be expected to produce the same clinical result as [Eylea] in any given patient," and that Yesafili is "interchangeable" with Eylea, see PTX-3097, as well as the Defendants' statements via a consultant's presentation at a medical conference that they had "demonstrated therapeutic equivalence of [Yesafili] and [Eylea] in the treatment of diabetic macular edema (DME)," that Yesafili "was safe and well tolerated, with a similar safety and immunogenicity profile to . . . Eylea," and that "[f]ollowing regulatory approval, [Yesafili]

is expected to be a new treatment option for patients with DME," see PTX-331.

For these reasons, the Court concludes that Regeneron has demonstrated by a preponderance of the evidence that, if the Defendants were to market their BLA Product, they would induce infringement of the asserted claims of the Treatment Patents.

C. Invalidity of the Patents-in-Suit

According to the Defendants, the asserted claims are anticipated, obvious, or invalid under 35 U.S.C. § 112. Specifically, the Defendants contend the asserted claims of the Product Patent are anticipated by Dix '226; obvious in light of three combinations of prior art references: (1) Fraser and Lucentis, (2) Fraser and Lui, and (3) Dix '226 alone; and invalid under § 112 because they are indefinite, lack written description, and lack enablement.

As to the Asserted Treatment Claims, the Defendants assert that Claim 6 of the '572 Patent, (the angiogenic eye disorder claim) is anticipated by Dixon or is obvious in view of Dixon alone or in combination with Hecht. They further assert that Claim 6 is invalid under § 112 for lack of written description and enablement.

The Defendants also assert that claims 25 of the '572 Patent and claim 11 or the '601 Patent (the DME claims) and claim 19 of

the '601 Patent (the DR claim) are anticipated by Regeneron's September 2009 press release or are rendered obvious in view of the '747 Patent, the 9-14-2009 Press Release, and in combination with Do 2009 and Lalwani 2009b. They further assert that these claims are invalid under § 112 for lack of written description and enablement.

1. Legal Standards

In 2011, Congress passed the America Invents Act ("AIA"), which changed the United States patent system from a "first to invent" system to a "first inventor to file" system. See Madstad Eng'g, Inc. v. U.S. Pat. & Trademark Off., 756 F.3d 1366, 1368 (Fed. Cir. 2014). Where, as here, the claims have an effective filing date prior to March 16, 2013, pre-AIA 35 U.S.C. § 102 applies. Blue Calypso, LLC v. Groupon, Inc., 815 F.3d 1331, 1341 n.4 (Fed. Cir. 2016); Solvay S.A. v. Honeywell Int'l Inc., 742 F.3d 998, 1000 n.1 (Fed. Cir. 2014) (noting that the "AIA amendments apply only to applications and patents with an effective filing date of March 16, 2013, or later"). Thus, the Court's citations to 35 U.S.C. §§ 102, 103, or 112 shall be in reference to the pre-AIA versions of the statute, unless expressly stated otherwise.

In all cases, each asserted claim is presumed to be valid. See 35 U.S.C. § 282; Microsoft Corp. v. I4i Ltd. P'ship, 564 U.S. 91, 94 (2011); Novo Nordisk A/S v. Caraco Pharm. Lab'ys, Ltd., 719 F.3d 1346, 1352 (Fed. Cir. 2013). The Defendants thus bear the burden of proving invalidity by clear and convincing evidence. See 35 U.S.C. § 282 ("The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity."); Microsoft, 564 U.S. at 102 ("[A] defendant raising an invalidity defense [bears] a heavy burden of persuasion, requiring proof of the defense by clear and convincing evidence." (citation and quotation marks omitted)). "[A] patentee never must submit evidence to support . . . that a patent remains valid . . . ." Prometheus Labs., Inc. v. Roxane Labs., Inc., 805 F.3d 1092, 1101–02 (Fed. Cir. 2015) (emphasis in original) (quoting Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1360 (Fed. Cir. 2007)). "Clear and convincing evidence places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting Colorado v. New Mexico, 467 U.S. 310, 316 (1984)).

a. Anticipation

A patent claim is invalid for anticipation when subject matter that the claims cover "was patented or described in a printed

publication . . . more than one year prior to the date of application for patent in the United States." 35 U.S.C. § 102(b); Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc., 855 F.3d 1356, 1367 (Fed. Cir. 2017); Net MoneyIN, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1369 (Fed. Cir. 2008). Whether a prior art reference anticipates a claim is a question of fact. Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 995 (Fed. Cir. 2006).

To prove anticipation, a defendant must show not only that a single reference "disclose[s] all elements of the claim within [its] four corners," but "all elements of a claimed invention arranged as in the claim." Net MoneyIN, 545 F.3d at 1369-71 (emphasis in original) (internal quotation marks omitted). A patent thus is invalid for anticipation if "a single prior art reference discloses each and every limitation of the claimed invention." Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003).

"[I]t is not enough that the prior art discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." Net MoneyIN, 545 F.3d at 1371; see also, e.g., Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323, 1334-35 (Fed. Cir. 2008); Union Oil Co. of Cal. v. Atl. Richfield Co., 208 F.3d 989,

995 (Fed. Cir. 2000). "[A]ll of the limitations" must be "arranged or combined in the same way as recited in the claim" in order to "prove prior invention of the thing claimed and . . . anticipate under 35 U.S.C. § 102." Net MoneyIN, 545 F.3d at 1371.

An anticipatory reference must "clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." Sanofi-Synethelabo v. Apotex, Inc., 550 F.3d 1076, 1083 (Fed. Cir. 2008) (quoting In re Arkley, 455 F.2d 586, 587 (C.C.P.A. 1972) (emphasis in original)). The reference must also "enable one of ordinary skill in the art to make the invention without undue experimentation." In re Gleave, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quoting Impax Labs., Inc. v. Aventis Pharms. Inc., 545 F.3d 1312, 1314 (Fed. Cir. 2008)).

b. Obviousness

A claimed invention is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (pre-AIA). "Obviousness is a question of law based on

underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." Osram Sylvania, Inc. v. Am. Induction Techs., Inc., 701 F.3d 698, 706 (Fed. Cir. 2012) (citing Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17–18 (1966)); see also KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 406–07 (2007) ("[T]he [Graham] factors continue to define the inquiry that controls."). "The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim." Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1086 (Fed. Cir. 2008). A party alleging obviousness based on a combination of prior-art references generally must prove by clear and convincing evidence both "[(1)] that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and [(2)] that the skilled artisan would have had a reasonable expectation of success from doing so." Cyclobenzaprine, 676 F.3d at 1068–69 (quoting Procter & Gamble, 566 F.3d at 994).

In considering the POSA's reasons or motivations to make or use the claimed invention, "a reference 'must [be] considered for all it taught, disclosures that diverged and taught away from the invention at hand as well as disclosures that pointed toward and

taught the invention at hand.'" Polaris Indus., Inc. v. Arctic Cat, Inc., 882 F.3d 1056, 1069 (Fed. Cir. 2018) (quoting Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 296 (Fed. Cir. 1985)); see also Arctic Cat Inc. v. Bombardier Recreational Prods. Inc., 876 F.3d 1350, 1363 (Fed. Cir. 2017) ("Evidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine.").

A patentee can refute an allegation that the POSA would have had a motivation or reason to make or use the claimed invention by showing that a particular prior art reference "taught away" from the invention. See Rembrandt Wireless Techs., LP v. Samsung Elecs. Co., 853 F.3d 1370, 1379-80 (Fed. Cir. 2017) ("[A] showing that a prior art reference teaches away from a given combination is evidence that one of skill in the art would not have been motivated to make that combination to arrive at the claimed invention."). A reference teaches away from the claimed invention if the POSA, "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken in the claim." AstraZeneca v. Mylan Pharm. Inc., 19 F.4th 1325, 1337 (Fed. Cir. 2021) (quoting Meiresonne v. Google, Inc., 849 F.3d 1379, 1382 (Fed. Cir. 2017)). The reference need not explicitly disparage an invention or address an aspect of the invention recited specifically in the claim to

teach away. See id.; see also, e.g., Arctic Cat Inc., 876 F.3d at 1360; Institut Pasteur & Universite Pierre et Marie Curie v. Focarino, 738 F.3d 1337, 1345-46 (Fed. Cir. 2013) (finding that a prior-art suggestion of a risk of toxicity precluded a conclusion of obviousness regardless of whether the claims recited a lack of toxicity). Whether the prior art "teaches away" is a question of fact. See Bombardier Recreational Prods. Inc., 876 F.3d at 1360; see also, e.g., Spectralytics, Inc. v. Cordis Corp., 649 F.3d 1336, 1343 (Fed. Cir. 2011), abrogated on other grounds by Halo Elecs., Inc. v. Pulse Elecs., Inc., 579 U.S. 93 (2016).

A claimed invention that is merely one of a "finite number of identified, predictable solutions," may be obvious if it was "obvious to try." KSR, 550 U.S. at 421. But "[t]o the extent an art is unpredictable, . . . KSR's focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." Eisai Co. v. Dr. Reddy's Labs., 533 F.3d 1353, 1359 (Fed. Cir. 2008). If "the prior art, at best, [gives] only general guidance as to the particular form of the claimed invention or how to achieve it, relying on an obvious-to-try theory to support an obviousness finding is impermissible." Cyclobenzaprine, 676 F.3d at 1073 (internal quotation marks omitted) (quoting In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009)). An invention is not

"obvious to try" if the prior art "gave no direction as to which of the many possible combination choices were likely to be successful" and "consistently taught away" from the claimed invention. Leo Pharm. Prods., Ltd. v. Rea, 726 F.3d 1346, 1357 (Fed. Cir. 2013).

Proving obviousness also requires a showing by clear and convincing evidence that the POSA would have had a reasonable expectation of success in achieving the claimed invention. InTouch Techs., Inc. v. VGO Commc'ns, Inc., 751 F.3d 1327, 1347 (Fed. Cir. 2014); see, e.g., Cyclobenzaprine, 676 F.3d at 1068–69. To have such an expectation, the POSA must have been "motivated to do more than merely to 'vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.'" Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)).

As with the POSA's reason for modifying or combining the prior art, the POSA's expectation of success must be assessed with respect to the actual needs in the pertinent art. See KSR, 550 U.S. 398 (focusing on motivation based on demands "present in the marketplace"); Institut Pasteur, 738 F.3d at 1345–46; Endo Pharms.

Sols., Inc. v. Custopharm Inc., 894 F.3d 1374, 1385 (Fed. Cir. 2018). Thus, in assessing whether the POSA would have had a reasonable expectation of success, a factfinder must determine whether the POSA would have believed that the invention would succeed based on the goals that the POSA would have had, regardless of whether those goals are recited as claim limitations. See, e.g., Institut Pasteur, 738 F.3d at 1345-46 (POSA would not have had a reasonable expectation of practicing a method of manipulating a living cell based on prior art references stating that such a method would be toxic to the cell, even though the claims did not expressly require that the cell remain viable).

The use of hindsight is prohibited in the obviousness analysis. KSR, 550 U.S. at 421 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning."). This is because the obviousness inquiry is conducted from the perspective of the POSA as of the priority date. Graham, 383 U.S. at 36 (courts must "resist the temptation to read into the prior art the teachings of the invention at issue"); Metalcraft of Mayville, Inc. v. Toro Co., 848 F.3d 1358, 1367 (Fed. Cir. 2017) ("[W]e cannot allow hindsight bias to be the thread that stitches together prior art patches into something that is the claimed invention."); Dey, L.P. v. Teva Parenteral Medicines, Inc., 6 F.Supp.3d 651,

673-74 (N.D. W.Va. 2014). "[T]he proper analysis requires a form of amnesia that 'forgets' the invention and analyzes the prior art and understanding of the problem at the date of the invention." Mintz v. Dietz & Watson, Inc., 679 F.3d 1372, 1379 (Fed. Cir. 2012). As the Federal Circuit has explained, "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art." Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1296 (Fed. Cir. 2012). Indeed, "the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." Life Techs., Inc. v. Clontech Labs., Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000); see also 35 U.S.C. § 103(a) (pre-AIA) ("Patentability shall not be negatived by the manner in which the invention was made.").

Objective indicia of non-obviousness must be considered where present. Cyclobenzaprine, 676 F.3d at 1075-76, 1079. Such evidence can help to "guard against slipping into use of hindsight" and "the temptation to read into the prior art the teachings of the invention at issue." Apple Inc. v. Samsung Elecs. Co., 839 F.3d 1034, 1052 (Fed. Cir. 2016) (en banc) (quoting Graham, 383 U.S. at 36); see also WBIP LLC v. Kohler Co., 829 F.3d 1317, 1328 (Fed. Cir. 2016) ("[O]bjective indicia of non-obviousness play an

important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis."); AstraZeneca AB v. Aurobindo Pharma Ltd., 232 F. Supp. 3d 636, 649 n.8 (D. Del. 2017) ("Because Aurobindo has failed to establish a prima facie case of obviousness, the court does not address AstraZeneca's secondary considerations."); Takeda Pharm. Co. v. Handa Pharm., 2013 WL 9853725, at *66 (N.D. Cal. Oct. 17, 2013) ("[T]he absence of secondary considerations does not prove obviousness.").

Evidence of an invention's unexpected properties, that the invention met a long-felt need, that the invention received industry praise, that others failed to solve the problems addressed by the invention, and that others have copied the invention all can serve as such objective indicia in support of non-obviousness. See, e.g., WBIP, 829 F.3d at 1332-37; Mintz, 679 F.3d at 1379-80. Likewise, "[e]vidence of industry skepticism weighs in favor of non-obviousness." WBIP, 829 F.3dat 1336 ("Doubt or disbelief by skilled artisans regarding the likely success of a combination or solution weighs against the notion that one would combine elements in references to achieve the claimed invention."). Objective indicia of nonobviousness also may consist of evidence that a prior art reference taught away from the claimed invention, i.e., that "person of ordinary skill, upon reading the reference, would be discouraged from following the

path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Millennium Pharm., Inc. v. Sandoz Inc., 862 F.3d 1356, 1366 (Fed. Cir. 2017) (quoting In re Urbanski, 809 F.3d 1237, 1244 (Fed. Cir. 2016)).

c. Section 112

The first paragraph of 35 U.S.C. § 112 states that the "specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, ¶ 1 (emphasis added). This section protects the public interest by enforcing the basic quid pro quo of the patent monopoly, ensuring the inventor possessed what is claimed as the invention at the time of filing (written description), and gave a disclosure where one of ordinary skill can make and use the full scope of the claimed invention without undue experimentation (enablement). Amgen Inc. v. Sanofi, 143 S. Ct. 1243, 1254 (2023); AK Steel Corp. v. Sollac & Ugine, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (an adequate disclosure in the specification is "part of the quid pro quo of the patent bargain"). Every patent specification must comply with both requirements. See AbbVie Deutschland GmbH

& Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1298 (Fed. Cir. 2014) ("drafters of patent applications know that they must describe their inventions as well as disclose how to enable their use"); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Both written description and enablement must be proven by clear and convincing evidence. Invitrogen Corp. v. Clontech Lab'ys, Inc., 429 F.3d 1052, 1072 (Fed. Cir. 2005).

Section 112 also requires the patent applicant to conclude the specification with "one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2.

i. Written Description

The written description requirement § 112 provides that a patent specification must "contain a written description of the invention, and of the manner and process of making and using it." 35 U.S.C. § 112 ¶ 1 (pre-AIA). The "hallmark" of an adequate written description is "disclosure." Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). The patent must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Id.

The relevant inquiry — "possession as shown in the disclosure" — is an "objective inquiry into the four corners of the

specification from the perspective of a person of ordinary skill" where "the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." Ariad, 598 F.3d at 1351. Possession is shown "by describing the invention, with all its claimed limitations." Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997). The patent's specification is not required to have "either examples or an actual reduction to practice; rather, the critical inquiry is whether the patentee has provided a description that in a definite way identifies the claimed invention in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing." Alcon Rsch. Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1190-91 (Fed. Cir. 2014) (internal quotation marks omitted) (quoting Ariad, 598 F.3d at 1350).

The written description requirement prevents an applicant from overreaching by later asserting that he invented something he did not actually invent. See Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1330 (Fed. Cir. 2003); Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1327 (Fed. Cir. 2000). It ensures that the "patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is

claimed." LizardTech, Inc. v. Earth Res. Mapping, Inc., 424 F.3d 1336, 1344-45 (Fed. Cir. 2005).

ii. Enablement

Under § 112, a patent specification also must "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112 ¶ 1 (pre-AIA). "To prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without 'undue experimentation.'" Alcon, 745 F.3d at 1188 (quoting In re Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988)). That some experimentation is necessary does not mean that a claim is not enabled. In re Wands, 858 F.2d at 736-37. The "key word is 'undue,' not experimentation." Id.

"The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1360 (Fed. Cir. 1998) (quoting PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996)).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." Id. at 737. These include the following "Wands" factors:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id.

"[T]he question is whether undue experimentation is required to make and use the full scope of embodiments of the invention claimed." McRO, Inc. v. Bandai Namco Games Am. Inc., 959 F.3d 1091, 1100 (Fed. Cir. 2020). The Supreme Court recently reiterated that:

> If a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person skilled in the art to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.

Amgen, 143 S. Ct. at 1254. When a patent specification has a broad disclosure, it is not required that every embodiment covered by the claims be exemplified; "it may suffice to give an example (or a few examples) if the specification also discloses 'some general quality . . . running through' the class that gives it a 'peculiar

fitness for the particular purpose.'" Id. A "specification may call for a reasonable amount of experimentation to make and use a patented invention. What is reasonable in any case will depend on the nature of the invention and the underlying art." Id. at 1255. But the person of ordinary skill in the art cannot be left with merely "a hunting license" or obligated to engage in "painstaking experimentation" or "trial and error" to "see what works." Id. at 1254, 1256-57. Whether a specification enables the full scope of the claimed invention is "determined as of the effective filing date of the patent's application." Alza Corp. v. Andrx Pharms., LLC, 603 F.3d 935, 940 (Fed. Cir. 2010).

iii. Indefiniteness

A claim is invalid as indefinite if, when read in light of the specification and prosecution history, the claim "fail[s] to inform, with reasonable certainty, those skilled in the art about the scope of the invention." Nautilus, Inc. v. Biosig Instruments, Inc., 572 U.S. 898, 901 (2014); 35 U.S.C. § 112 ¶ 2 (pre-AIA). While definiteness "mandates clarity," the Supreme Court has recognized that "absolute precision is unattainable." Nautilus, 572 U.S. at 910. "One must bear in mind . . . that patents are 'not addressed to lawyers, or even to the public generally,' but rather to those skilled in the relevant art." Id. at 909 (quoting Carnegie Steel Co. v. Cambria Iron Co., 185 U.S. 403, 437 (1902)).

Accordingly, "[c]laims reciting terms of degree 'have long been found definite' if they provide reasonable certainty to a skilled artisan when read in the context of the patent." Mentor Graphics Corp. v. EVE-USA, Inc., 851 F.3d 1275, 1290 (Fed. Cir. 2017) (quoting Biosig Instruments, Inc. v. Nautilus, Inc., 783 F.3d 1374, 1378 (Fed. Cir. 2015)). Definiteness "is to be evaluated from the perspective of someone skilled in the relevant art" at the time the patent was filed." Nautilus, 572 U.S. at 908.

2. Invalidity of the Product Patent

a. Dix '226 Does Not Anticipate the Product Patent

The Defendants argue anticipation of the asserted claims of the Product Patent based on Dix '226 (U.S. Patent No. 10,406,226 B2), a patent assigned to Regeneron and issued on September 10, 2019. DTX-13. Dix '226 is directed to formulations of VEGF antagonists for cancer. Dix '226 does not include any teaching of an "ophthalmic formulation[s]" or intravitreal administration, to which the Product Patent claims are directed. To the contrary, Dix '226 only teaches that VEGF is involved in cancer. DTX-13, 1:42-54; Tr. 1123:25-1124:11 (Rabinow).

The Court finds that Dix '226 does not anticipate the Asserted Claims of the Product Patent. Dix does not anticipate the Product Patent because it does not disclose 40 mg/ml aflibercept, the

concentration required by every asserted claim of the Product Patent.

The Defendants argued that 40 mg/ml aflibercept claim requirement is satisfied by the disclosure in Dix '226 of "10-50 mg/ml of the fusion protein." DTX-13, 2:23; Tr. 1083:15-18 (Rabinow); see also DTX-13, 7:8-9. The Defendants' expert, however, admitted that 40 mg/mL is not expressly disclosed by the range of "10-50 mg/ml." Tr. 1133:25-1134:3 (Rabinow). Moreover, the range of 10-50 mg/ml is not a small range. Dr. Rabinow's testimony made clear that "10-50 mg/ml" includes not just every whole-number value from 10 to 50, but also includes more precise values to the tenths and hundredths decimal places—like "37.2" and "49.35" mg/ml—resulting in thousands of discrete values within the disclosed range. Tr. 1135:25-1138:9. Dr. Trout also testified that the range was not a small one. Tr. 2072:16-17 (Trout).

Furthermore, the disclosure in Dix '226 of "10-50 mg/ml" is not linked to aflibercept specifically, but instead refers to a generic "VEGF-specific fusion protein antagonist." DTX-13 at 2:20-23. The Defendants' expert did not dispute that multiple fusion proteins would fall within that genus. Dr. Rabinow explained that the recited "fusion protein" is not limited to aflibercept but instead covers a "class" of proteins, Tr. 1135:25-1138:9, and Dr. Trout agreed, Tr. 2073:13-2074:4. Notably, Dix

'226 identifies at least two such fusion proteins by sequence, and more would fall within the class. DTX-13 at 2:3-19. As Dr. Rabinow agreed, only the aflibercept fusion protein falls within the asserted claims; the other fusion proteins encompassed by Dix's disclosed class do not meet the limitations of the Product Patent. Tr. 1136:14-1138:2. Thus, the Defendants' argument based on "Dix '226's disclosed aflibercept protein range of 10 to 50 mg/ml" (ECF No. 576 (Defs.' Opening Br.) at 22 (emphasis added)) incorrectly describes Dix's disclosed genus. The disclosure in Dix '226 of "10-50 mg/ml of the fusion protein" refers to a large range of numerical concentrations and also encompasses multiple different fusion proteins — and yet, only one such concentration (40 mg/ml) and one such fusion protein (aflibercept) meets the asserted claims of the Product Patent. The evidence does not support the Defendants' argument that Dix's broad genus of "10-50 mg/ml of the fusion protein" discloses 40 mg/ml of aflibercept. As a result, the Defendants have not proven the legal requirements of anticipation as to Dix '226.

Nor is this a case of "overlapping ranges" giving rise to a "prima facie case of anticipation." Defs.' Opening Br. 22. Each asserted claim recites the specific concentration of 40 mg/ml aflibercept, not a range of concentrations. As explained below, the Defendants also are incorrect in arguing that Regeneron must

prove that 40 mg/ml is "'critical to the operability' of the invention." Defs.' Opening Br. 22. In any event, the testimony at trial demonstrated that the inventors specifically chose the 40 mg/ml concentration to maximize the half-life of aflibercept in the eye while minimizing toxicity and stability concerns, see, e.g., Tr. 473:2-22 (Furfine); Tr. 1680:12-1682:1, 1780:18-20 (Graham), and their selection of 40 mg/ml contributed to the beneficial properties of Eylea, see Tr. 493:10-494:7, 495:16-21 (Furfine). No record evidence shows that these desirable benefits of the claimed invention would obtain at other concentrations between 10 and 50 mg/ml. Accordingly, even if anticipation law required a showing of criticality in the present situation, undisputed evidence at trial demonstrates that the 40 mg/ml concentration of aflibercept is critical to the benefits provided by the claimed invention.

In their post-trial briefing, the Defendants state that Dix '226 disclosed a "'40 mg/ml' embodiment." Defs.' Opening Br. 4 (citing DTX-13, 3:60-61). The Defendants' characterization of this disclosure is incorrect, and their reliance on it is forfeited. Dix refers to "a 40 mg/ml pre-lyophilized solution [that] is lyophilized and reconstituted to a 80 mg/ml solution." DTX-13, 3:60-62. Dr. Trout offered unrebutted testimony that a pre-lyophilized solution is only "a manufacturing intermediate"

not intended for any kind of injection. Tr. 2077:1-16. Dr. Trout's testimony is consistent with the disclosure of Dix, which states that the pre-lyophilized solution "is lyophilized and reconstituted" to a different concentration; Dix does not disclose the pre-lyophilized solution as being stored or injected. DTX-2, 3:60-61. Dr. Trout also explained that Dix did not teach that the "pre-lyophilized solution" included aflibercept, and that the POSA would not expect this manufacturing intermediate to meet the 98% native conformation limitation over two months, as a formulator would not "store it for nearly that long." Tr. 2077:17-2079:1. Thus, Dix's "40 mg/ml pre-lyophilized solution" does not refer to any kind of formulation to be administered, much less an ophthalmic formulation or, as the claim requires, an ophthalmic formulation of aflibercept.

In any event, the arguments in the Defendants' opening brief involving anticipation over Dix '226 never reference Dix's "40 mg/ml pre-lyophilized solution" disclosure, Defs.' Opening Br. 22-23, and so the Court holds that any reliance on that passage has been forfeited. See Vanda Pharms., Inc. v. Teva Pharms. USA, Inc., 2022 WL 17593282, at *12 n.1 (D. Del. Dec. 13, 2022) (holding that a party "forfeited its right" to raise a specific argument "by not raising it in timely fashion" and "by the passing manner in which it raised the argument in its post-trial brief"), aff'd, 2023 WL

3335538 (Fed. Cir. May 10, 2023). Furthermore, Dr. Rabinow did not disclose any reliance on the pre-lyophilized solution in his expert reports, and indeed never even addressed it. PTX-55 ¶¶ 122-27, 245-59.

To prove anticipation, a defendant must prove that a single prior art reference discloses every limitation of the claim. Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006). "It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus." Id.; see also UCB, Inc. v. Actavis Labs., 65 F.4th 679, 688 (Fed. Cir. 2023) ("[T]he disclosure of a range is not a disclosure of the endpoints of the range or other discrete points within the range."); Janssen Pharms. v. Watson Labs., 2012 WL 3990221, at *9 (D.N.J. Sept. 11, 2012) (same); OSRAM Sylvania v. Am. Induction Techs., 701 F.3d 698, 705-06 (Fed. Cir. 2012) (same).

As relevant here, "the disclosure of a range is not a disclosure of the endpoints of the range or other discrete points within the range." UCB, Inc. v. Actavis Labs., 65 F.4th 679, 688 (Fed. Cir. 2023). A numerical range is a genus encompassing the values within it, Janssen, 2012 WL 3990221, at *7 (holding "dosage range in [prior art] is a genus"), and only "a very small genus" may anticipate specific intervening values, Atofina, 441 F.3d at

999. For example, the Federal Circuit's predecessor court concluded that disclosure of a genus of "20 possible compounds" with similar structures and properties could anticipate a species within the genus. In re Ruschig, 343 F.2d 965, 973-74 (C.C.P.A. 1965) (discussing In re Petering, 301 F.2d 676 (C.C.P.A. 1962)). The Defendants failed to establish that the five-fold range of 10-50 mg/ml disclosed in Dix '226 (DTX-13) is "very small." Atofina, 441 F.3d at 999. Rather, in Dr. Rabinow's view, this range encompasses hundreds of discrete concentrations between 10 and 50 (like "28" mg/ml, "37.2" mg/ml, and "49.35" mg/ml). Tr. 1134:9-19; see Atofina, 441 F.3d at 999 ("A temperature range of over 100 degrees is not a small genus."); Tr. 2072:16-17 (Trout).

The genus is further enlarged by the fact that Dix's range is not limited to aflibercept, but rather covers a broader generic set of "VEGF-specific fusion protein antagonist" molecules, both sides' expert agreed. Tr. 1135:25-1138:9 (Rabinow); Tr. 2073:13-2074:4 (Trout). Nor does Dix '226 disclose any formulation with 40 mg/ml aflibercept that meets the 98% native conformation limitation, or any ophthalmic formulation, also required by each claim, which separately is fatal to the Defendants' anticipation argument. See Tr. 1124:9-11, 1124:25-1125:16 (Rabinow); e.g., Atofina, 441 F.3d at 999 ("single reference" must disclose "each limitation"). Because Dix '226 does not disclose what the claims

require specifically — 40 mg/ml of aflibercept, with 98% native conformation after two months storage at 5°C—it cannot anticipate the claims.

Thus, the Defendants' anticipation theory involves the POSA arbitrarily and improperly selecting 40 mg/ml from the range of 10-50 mg/ml and cobbling together other, disparate disclosures from Dix '226. But to anticipate, the prior-art reference must disclose each element "arranged as in the claim." Net MoneyIN, Inc. v. Verisign, Inc., 545 F.3d 1359, 1370-71 (Fed. Cir. 2008). The Defendants' "mechanistic dissection and recombination" of disclosures from Dix '226 involves just the kind of impermissible "hindsight anticipation[]" relying on "the guidance of a[] [patentee's] disclosures" that precedent has long forbid. Ruschig, 343 F.2d at 974.

Following that precedent, the Janssen court rejected an anticipation argument indistinguishable from the one the Defendants raise here, concluding that a dosage range of ".02-0.05 mg" did not anticipate a specific dose of "0.025 mg." 2012 WL 3990221, at *6-10. The Court's holding in Janssen is consistent with Federal Circuit precedent explaining that where "[t]he disclosure is only that of a range, not a specific [point] in that range, . . . the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate

points." Atofina, 441 F.3d at 1000; UCB, 65 F.4th at 688. The Court holds likewise here that the range of 10-50 mg/ml in Dix '226 does disclose every intermediate point in the range, including 40 mg/ml.

As explained, the Defendants forfeited any reliance on the 40 mg/ml "pre-lyophilized solution" disclosed in Dix '226 by not relying on it in their post-trial brief. Furthermore, Dr. Rabinow did not disclose any reliance on the pre-lyophilized solution in his expert reports–indeed, he never even addressed it. PTX-55 (Rabinow Opening Report) ¶¶ 122-27, 245-59. The Court therefore strikes Dr. Rabinow's testimony as to the "40 mg/mL pre-lyophilized solution" portion of the prior art reference. See PersonalWeb Techs. LLC v. Int'l Bus. Machs. Corp., 2017 WL 8186294, at *6 (N.D. Cal. July 25, 2017) (excluding expert opinion on claim limitation at trial that was not disclosed in expert report).

In any event, the "pre-lyophilized solution" refers only to a "manufacturing intermediate," not a formulation for administration, and Dix '226 does not indicate whether the pre-lyophilized solution contains aflibercept or any other limitation of the claims. Tr. 2077:1-16 (Trout). Thus, even if considered, the isolated disclosure of 40 mg/ml pre-lyophilized solution, unconnected to any of the other claim elements, is not a disclosure

of each element "arranged as in the claim." Net MoneyIN, 545 F.3d at 1370.

The Defendants also argue that Regeneron must show criticality of the claimed aflibercept concentration. Defs.' Opening Br. 22. However, the Federal Circuit has held that criticality is a factor only where a disclosed range "overlaps" with a "claimed range," not a specific point. Genentech, Inc. v. Hospira, Inc., 946 F.3d 1333, 1338 (Fed. Cir. 2020) (emphasis added). Furthermore, the Federal Circuit has specifically rejected equating "discrete points" in a range with a range itself. UCB, 65 F.4th at 687-88. The Product Patent claims a specific concentration — 40 mg/ml — not a "claimed range." The Defendants cite no case where a court considered criticality in an anticipation inquiry under these circumstances.

The Court concludes that criticality is thus irrelevant here — consistent with Janssen, 2012 WL 3990221, at *6-10, which addressed indistinguishable facts and also did not consider criticality — as well as with numerous other precedents addressing anticipation in the genus/species context. See Ruschig, 343 F.2d at 974 (not considering criticality in anticipation context of whether genus anticipates species); Mylan Pharm. Inc. v. Merck Sharp & Dohme Corp., 50 F.4th 147, 153-54 (Fed. Cir. 2022) (same); Eli Lilly & Co. v. Bd. of Regents of Univ. of Washington, 334 F.3d

1264, 1271-72 (Fed. Cir. 2003) (same); Bristol-Myers Squibb Co. v. Ben Venue Labs., 246 F.3d 1368, 1380 (Fed. Cir. 2001) (same); Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., 687 F. Supp. 2d 486, 499 (D. Del. 2010), aff'd, 655 F.3d 1291 (Fed. Cir. 2011) (same).

Nonetheless, even if criticality were relevant, the Court concludes that Regeneron has demonstrated criticality of the 40 mg/ml concentration, because the prior art taught away from using that concentration and because Regeneron demonstrated unexpected properties of the claimed compositions, as described further below. See Cot'n Wash, Inc. v. Henkel Corp., 56 F. Supp. 3d 626, 644 (D. Del. 2014) (finding criticality based on unexpected results and teaching away).

For these reasons, the Court concludes that Mylan has failed to demonstrate by clear and convincing evidence that Dix '226 anticipates the asserted clams of the Product Patent.

b. The Defendants Combinations of Prior Art do not Render the Product Patent Obvious

To prove obviousness, the Defendants must show by clear and convincing evidence that the differences between the claims "and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made" to the POSA. 35 U.S.C. § 103(a) (pre-AIA). Here, the asserted claims all

require an ophthalmic formulation of the VEGF antagonist aflibercept at a concentration of 40 mg/ml. As explained further below, in the prior art cited by the Defendants, the only disclosure of a 40 mg/ml formulation taught the POSA away from using that concentration for aflibercept because it would lead to unacceptable inflammation without any advantages. That teaching forecloses obviousness. AstraZeneca v. Mylan, 19 F.4th at 1336 (teaching away "on its own is sufficient to sustain" nonobviousness); Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000) (teaching away "finding alone can defeat" nonobviousness). Furthermore, the other evidence at trial, including Regeneron's objective evidence of nonobviousness, demonstrated that the inventions claimed in the Product Patent were not obvious.

i. The Defendants are limited to their disclosed obviousness combinations

As an initial matter, the Court rejects any attempt by the Defendants to rely on reference combinations never disclosed in discovery, or prior art that was never disclosed at all, consistent with the Court's ruling during trial. Tr. 796:14-797:6 (precluding obviousness opinion as to Fraser, Dix, and Lucentis); see ECF Nos. 529, 540. As the Court explained, "the Federal Circuit has been abundantly clear . . . that when we're talking about obviousness,

the specific prior art needs to be identified and then an explanation needs to be identified in the expert disclosures," Tr. 996:16-997:1; the Court will not "tie . . . together" reference combinations that the Defendants themselves did not timely disclose, Tr. 1075:17-22. See Innogenetics, N.V. v. Abbott Labs., 512 F.3d 1363, 1373 (Fed. Cir. 2008); ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc., 694 F.3d 1312, 1327-28 (Fed. Cir. 2012) (deeming obviousness opinion insufficient where expert "failed to explain how specific references could be combined, which combination(s) of elements in specific references would yield a predictable result, or how any specific combination would operate or read on the asserted claims"); Changzhou Kaidi Elec. Co. v. Okin Am., Inc., 112 F. Supp. 3d 330, 334 (D. Md. 2015) (excluding expert opinion asserting "previously undisclosed combinations of those same prior art references," enforcing rules requiring the defendants to identify expressly "any combinations of prior art showing obviousness"); see also S. States Rack & Fixture, Inc. v. Sherwin-Williams Co., 318 F.3d 592, 596 (4th Cir. 2003).

When the Defendants sought to rely on another undisclosed combination (Lucentis and Liu), the Court again sustained Regeneron's objection. Tr. 1045:23-1048:7, 1074:20-1075:22. And just as trial was not the place for new obviousness theories and combinations, the Court rejects any effort by the Defendants to

circumvent the Courts' rulings at trial by relying on undisclosed references, combinations, or prior art theories in their post-trial briefing, as set forth below.

a) Avery

The Court concludes that the Defendants did not disclose during discovery any obviousness theory relying on Avery (DTX-2264) to provide a motivation either to use a larger molecule for intravitreal injection or to use a higher concentration. The Court excludes any such theory. Even if the Court did consider it, however, it would not change the Court's rulings in favor of Regeneron as to the Product Patent.

b) "Background" References

In addition, the Court notes that several of the references the Defendants cite as "Background" reflect Regeneron's own work published less than a year before Regeneron's asserted June 16, 2006 priority date of the Product Patent. See DTX-4957 (Regeneron Form 10-K for fiscal year 2005); DTX-216 (internal Regeneron discussion dated March 21, 2006 regarding conference abstract). The Defendants did not disclose these references during discovery or pursuant to their statutory obligation under 35 U.S.C. § 282 as

relevant prior art to the Product Patent, which precluded their use at trial.

c) Ferrara 2005

Dr. Rabinow also offered testimony regarding a separate Ferrara reference ("Ferrara 2005," DTX-4041) concerning a Phase 3 ranibizumab study. Tr. 1031:3-6 (Rabinow). Regeneron objected to this line of testimony as outside the scope of Dr. Rabinow's report. Id. Regeneron explained that Dr. Rabinow never identified Ferrara 2005 as a prior art reference or discussed it in detail. Tr. 1031:08-1032:18 (Rabinow). Dr. Rabinow discussed forty-six references in the background of his opening report, see generally PTX-55 (Rabinow Opening Report) ¶¶ 96-176, but the Ferrara 2005 reference is not identified there. He then identified four combinations of certain of those prior art references that he asserted against Regeneron's claims. Again, these did not include Ferrara 2005. PTX-55 ¶ 180. Dr. Rabinow mentions Ferrara 2005 just twice in his "tutorial" about "VEGF Antagonists." PTX-55 ¶¶ 67-68.

The Defendants suggest that Dr. Rabinow can opine about the Ferrara 2005 reference because he referred generally to the results of Lucentis clinical trials published in other articles in his report. However, Dr. Rabinow did so only with respect to different

references concerning ranibizumab, not Ferrara 2005. That does not suffice to disclose an expert opinion under Rule 26. An expert cannot testify about obviousness based on a prior art reference that was not previously disclosed under Federal Rule of Civil Procedure 26. See Innogenetics, 512 F.3d at 1373; ActiveVideo Networks, 694 F.3d at 1327-28; Changzhou Kaidi Elec. Co., 112 F. Supp. 3d at 334. Thus, the Court will not consider Dr. Rabinow's testimony about the Ferrara 2005 reference as prior art. Tr. 1031:3-16 (Rabinow). Even if the Court did consider this reference, however, it would not change the Court's rulings Regeneron as to the Product Patent.

d) Rudge

Relatedly, the Court concludes that the Defendants did not meet their burden of proving that the Rudge reference (DTX-3592) is prior art to the Product Patent. Rudge's publication date is unclear from the record. Regeneron asserts Dr. Rabinow acknowledged on cross examination that Rudge cited "papers published after the June 16, 2006 priority date." Tr. 1147:11-15. Although the reference lists a copyright date of 2005, Dr. Rabinow agreed that it was "confusing" how a reference could both be published in 2005 yet cite to publications from after June 16, 2006. Tr. 1147:18-1148:3. The Defendants assert that this attack

is unwarranted because Dr. Rabinow explained that the fact that the Rudge paper has a publication date of 2005, but includes citations to references in 2006 is not surprising, because often versions of papers or abstracts are released online earlier than their official publication dates. (Tr. 1141:7-1143:11-15 (Rabinow)). And, most of the citations Regeneron pointed to were expressly identified as ARVO e-abstracts. (See, e.g., Tr. 1142:12-16; DTX 3592.5 (Brown citation of "IOVS 2006. 47: ARVO E-Abstract 2963"); DTX 3592.6 (Heier citation of "IOVS. 2006. 47: ARVO E-Abstract 2959")). In view of this conflicting evidence, the Court concludes the Defendants did not meet their burden of showing by clear and convincing evidence that Rudge is prior art. Sandt, 264 F.3d at 1350. Even if the Court did consider this reference, however, it would not change the Court's rulings in favor of Regeneron as to the Product Patent.

ii. Fraser and Lucentis

The Defendants' first obviousness argument relies on the combination of Fraser (DTX-729) and "Lucentis," i.e., Gaudreault (PTX-1839) and Shams (DTX-726). The Defendants argue that the POSA would have been motivated to replace the ranibizumab in either of the Lucentis references with aflibercept, which the Defendants contend was disclosed in Fraser.

As an initial matter, the Court disagrees with the Defendants that the POSA would necessarily have been motivated to replace one drug in a formulation with another in its class. The Defendants cite Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1483-84 (Fed. Cir. 1997) and Senju Pharm. Co. v. Lupin Ltd., 780 F.3d 1337, 1347 (Fed. Cir. 2015), but neither case stands for the "general proposition that a skilled artisan would always be motivated to try later generation compounds in an old composition." Apotex Inc. v. Wyeth LLC, 657 F. App'x 998, 1003 (Fed. Cir. 2016) (addressing Senju). Richardson-Vicks did not address formulations at all, but rather involved claims to a combination of two known drugs that the Federal Circuit concluded would have been obvious to combine based on the facts of the case. 122 F.3d at 1480-84.

Likewise, Senju (as the Federal Circuit confirmed in Apotex) also turned on the factual record in that case and the close structural similarity of the claimed compounds in the formulations of the prior art and the claims. 780 F.3d at 1346-47. In the particular context relevant here, Dr. Trout explained that the POSA would not just substitute one protein formulation for another, Tr. 2148:3-14; see Tr. 453:10-18 (Furfine) (explaining "[t]hat's not how we do formulation discovery"). Furthermore, Dr. Trout explained that fusion proteins are fundamentally different from antibodies in that fusion proteins are synthetic molecules made by

humans, while antibodies have evolved over time to be stable. Tr. 2013:14-17, 2014:21-2015:16; see also PTX-1835 (Fast) at 15 ("In comparison with native IgG proteins, wherein interdomain interactions presumably have evolved to provide mutual stabilization, fusion proteins may lack such stabilizing interdomain stabilization."); Tr. 448:1-6, 456:6-9 (Furfine).

a) Lucentis taught away from 40 mg/ml of a VEGF antagonist

A reference teaches away where a POSA "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken in the claim." AstraZeneca v. Mylan, 19 F.4th at 1337 (quoting Meiresonne v. Google, Inc., 849 F.3d 1379, 1382 (Fed. Cir. 2017)). Here, the prior art taught away from the claimed concentration of 40 mg/ml of glycosylated aflibercept. Specifically, the prior art both taught against "following the path set out in the reference," (using a 40 mg/ml formulation of a VEGF antagonist in an ophthalmic formulation) and "led [the POSA] in a direction divergent from the path that was taken in the claim" (40 mg/ml of aflibercept). AstraZeneca v. Mylan, 19 F.4th at 1337. Dr. Trout's testimony was that the "moderate to severe" inflammation exhibited after administration with 40 mg/ml ranibizumab taught away from using 40 mg/ml aflibercept. Tr.

2040:10-2041:10, 2041:22-2043:2, 2045:8-11 (Trout). Dr. Trout explained that the inflammation persisted for seven days and was "problematic from an immune response standpoint" and thus "would teach the [POSA] away from the 40 mg/ml." Tr. 2041:1-10. In contrast, the 10 mg/ml ranibizumab formulation did not exhibit such levels of inflammation, and the authors found that this lower "dose provides maximum inhibition of VEGF." Tr. 2041:22-2042:9; PTX-1839 at 7. Dr. Trout's analysis of Gaudreault was unrebutted by Dr. Rabinow, and is "conclusive" of teaching away. Raytheon, 993 F.3d at 1382 ("unrebutted evidence" on issue was "conclusive"); Imperium, 757 F. App'x at 978-79 (no reasonable basis to reject opinion of expert whose "testimony was not contradicted").

Moreover, it was undisputed that aflibercept was much more potent than ranibizumab. Tr. 2042:13-17 (Trout); Tr. 114:1-25 (Yancopoulos). Because of its higher potency, less aflibercept is needed to inhibit the same amount of VEGF as compared to ranibizumab. Critically, Gaudreault found that only 10 mg/ml of ranibizumab resulted in "maximum inhibition of VEGF," PTX-1839 at 7, and Dr. Trout explained that the POSA would have been motivated to use a concentration of aflibercept lower than the 10 mg/ml ranibizumab in view of aflibercept's higher potency and the greater risk of aggregation caused by a higher concentration, Tr. 2042:18-2043:2, 2044:5-22 (Trout); PTX-1556 (Wang 2005) at 9. Dr. Rabinow

again offered no contrary testimony, thus undermining the Defendants' argument that a POSA would use 40 mg/ml aflibercept. See Raytheon, 993 F.3d at 1382; Imperium, 757 F. App'x at 978-79. Thus, the Defendants have failed to point to any motivation in the prior art to use a 40 mg/ml formulation of aflibercept.

The Court is mindful that "the fact that there may be reasons a skilled artisan would prefer one [option] over the other does not amount to a teaching away from the lesser preferred but still workable option." Bayer Pharma AG v. Watson Labs., Inc., 874 F.3d 1316, 1327 (Fed. Cir. 2017). The unrebutted evidence at trial, however, demonstrated that the POSA would not have viewed the 40 mg/ml formulation merely as an inferior or unpreferred but nonetheless suitable option. To the contrary, the POSA would have been discouraged from the "path set out in" Gaudreault regarding a 40 mg/ml formulation, because it produced a problematic immune response without providing any advantage in VEGF inhibition, and because the POSA would have considered fusion proteins like aflibercept to have a higher risk of generating an immune response. AstraZeneca v. Mylan, 19 F.4th at 1337; Tr. 2040:23-2041:5, 2043:8-2044:4 (Trout).

Generating such an immune response would have been a fatal property for an ophthalmic formulation—as it was for Gaudreault's 40 mg/ml ranibizumab formulation, which undisputedly was never

developed further. Tr. 2042:10-12 (Trout); Tr. 549:11-22 (Furfine) (noting that Genentech "did not develop the 40 mg/ml formulation"). Indeed, the evidence at trial was unequivocal that "moderate to severe" inflammation was an extremely concerning phenomenon for any intravitreal drug product to exhibit, as it could result in vision loss and thus defeat the purpose of using an ophthalmic drug product in the first place. See Tr. 468:1-470:7 (Furfine) (the inflammation in the 40 mg/ml Gaudreault formulation was "substantial and concerning" and "unacceptable"); Tr. 549:1-2 (Furfine) ("[R]epeated moderate to severe inflammation might cause vision loss."); Tr. 115:16-20 ("[M]any drugs in this space have failed because they've caused what's called inflammation or other side effects leading to actual blindness. So the cure can be worse than the disease if you inject something that can almost immediately cause blindness."), 125:2-21 (Yancopoulos); Tr. 861:1-5 (Albini) (agreeing that "significant intraocular inflammation" occurred with a drug called abicipar, which then "did not make it to the market").

There was nothing in the prior art that would have pointed a POSA to the 40 mg/ml concentration absent hindsight in working backwards from the claimed invention. Thus, the Court concludes Gaudreault's teachings with respect to the 40 mg/ml concentration of a VEGF antagonist meet the standard for teaching away. See

Crocs, Inc. v. ITC, 598 F.3d 1294, 1308-09 (Fed. Cir. 2010) (finding teach away where prior art taught claimed material was "unsuitable"); Millennium, 862 F.3d at 1366-67 (holding that prior art taught away from modification where it "would have been unattractive to a person of ordinary skill for fear of disturbing the chemical properties whereby bortezomib functions effectively as an anti-cancer agent"); AstraZeneca v. Mylan, 19 F.4th at 1337 (prior art taught away where district court held that reference "cut against the very goal a [POSA] would have been trying to achieve—a stable product with a consistent dose").

The Defendants criticize the Product Patent on the basis that it "provides no additional motivation to overcome" the problems the prior art taught regarding high concentrations, citing Merck & Co., Inc. v. Teva Pharm., 395 F.3d 1364, 1373-74 (Fed. Cir. 2005). Defs.' Opening Br. 27. But the disclosure of the Product Patent's specification is not prior art; it is irrelevant to the motivation of the POSA and whether that prior art taught away from the invention. The role of the specification is not to review the prior art's failures or its teachings against the claimed invention, but rather to "disclose[] and teach[]" the invention and inform the POSA how to make and use it. Ariad, 598 F.3d at 1347.

There is no requirement for a patent to point out each instance where it deviates from the prior art, as the obviousness analysis forecloses reading the prior art through the lens of the patent with the benefit of hindsight. Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., 933 F.3d 1367, 1375 (Fed. Cir. 2019); ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546 (Fed. Cir. 1998). The Defendants' cited portions of Merck have nothing to do with teaching away or the POSA's motivation, but rather with differences between the prior art and the claims. 395 F.3d at 1373-74.

Similarly, the Federal Circuit has explained that "'[t]eaching away' does not require that the prior art foresaw the specific invention that was later made, and warned against taking that path." Spectralytics v. Cordis, 649 F.3d 1336, 1343 (Fed. Cir. 2011). What ultimately matters is whether the POSA, upon reading the prior art, would have been taught against taking the approach required by the claimed invention. AstraZeneca v. Mylan, 19 F.4th at 1337. And here, the unrebutted testimony demonstrated that the POSA would have been taught against using 40 mg/ml aflibercept.

Likewise, the Court rejects the Defendants' suggestion that the claims were required to recite explicitly the properties related to pharmacokinetics and inflammation in order to be relevant. The teaching-away analysis focuses on the motivation of

the POSA, without hindsight knowledge of the invention. And as the Federal Circuit has explained, that analysis may properly consider an "unclaimed feature" if it is relevant to the POSA's motivation to modify or combine the prior art to make the claimed invention. Chemours Co. FC v. Daikin Indus., Ltd., 4 F.4th 1370, 1377 (Fed. Cir. 2021). In AstraZeneca v. Mylan, for example, the prior art at issue contained data on formulations which displayed "drug adhesion" to the dispensing device and the POSA accordingly would have understood those formulations "were not suitable" and "clearly don't work." 19 F.4th at 1336. Because those formulations were similar to those claimed in the patent at issue and would have led the POSA away from making them, the Federal Circuit concluded that the prior art formulations showing drug adhesion taught away, id., even though the claims did not recite anything about drug adhesion, id. at 1328; see also Chemours, 4 F.4th at 1377 (prior art's teachings to a POSA regarding "unclaimed feature" of "molecular weight distribution" precluded motivation to combine); Institute Pasteur, 738 F.3d at 1345-46 (Board erred by not considering toxicity of proposed combination even though claims did not require viability or level of toxicity); cf. Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, 655 F.3d 1291, 1307 (Fed. Cir. 2011) ("Our case law is clear that the structure of a claimed compound and its properties are inseparable

for purposes of § 103."). Here, the asserted claims of the Product Patent require an aflibercept concentration of 40 mg/ml, and the evidence at trial showed that Gaudreault's inflammation result would have discouraged the POSA from making a 40 mg/ml composition. As in AstraZeneca v. Mylan, Institut Pasteur, and Chemours, that teaching is relevant (and here, dispositive) even though the claims do not recite inflammation levels.

The Court concludes that Gaudreault's teaching away from a 40 mg/ml concentration "on its own is sufficient to sustain the nonobviousness" of the claims. AstraZeneca v. Mylan, 19 F.4th at 1336; see Winner, 202 F.3d at 1349-50 (teaching away "finding alone can defeat" nonobviousness). The Court nonetheless analyzes below the remaining issues between the parties pertaining to obviousness.

b) Fraser did not motivate the POSA to make a 40 mg/ml formulation

There is no dispute that Fraser disclosed a composition having 24.3 mg/ml of a VEGF Trap that was used to investigate ovarian functions in monkeys. DTX-729 at 1-2. Dr. Rabinow agreed that "Fraser says not one word about injecting its formulation into the eye." Tr. 1103:1-3. He nonetheless offered testimony that the POSA would have converted Fraser's 24.3 mg/ml concentration for intravenous injection for ovarian function in monkeys into the 40

mg/ml concentration in the claimed ophthalmic formulations for intravitreal injection in humans. Tr. 1067:2-1068:15. The Court does not find Dr. Rabinow's testimony credible as his chain of inferences appear to be driven entirely by hindsight and to lack any support in the prior art's teachings or the knowledge of the POSA, and the Court likewise rejects the Defendants' other arguments pertaining to the 40 mg/ml limitation, for the reasons discussed above. Because the claimed subject matter "as a whole" must have been obvious, 35 U.S.C. § 103(a), and the Defendants have failed to establish by clear and convincing evidence that the 40 mg/ml concentration would have been obvious, the Defendants' obviousness challenge fails. E.g., Univ. of Strathclyde v. Clear-Vu Lighting LLC, 17 F.4th 155, 165-66 (Fed. Cir. 2021).

c) The art did not motivate using a protein as large as glycosylated aflibercept

The obviousness inquiry does not merely ask whether a skilled artisan could combine the references, but instead asks whether "they would have been motivated to do so." Adidas AG v. Nike, Inc., 963 F.3d 1355, 1359 (Fed. Cir. 2020) (quoting InTouch Techs., Inc. v. VGO Commc'ns, Inc., 751 F.3d 1327, 1352 (Fed. Cir. 2014)); Cyclobenzaprine, 676 F.3d at 1068-69. The Court concludes that the prior art would not have motivated the POSA to use a large

molecule like aflibercept because it would have been considered too large to reach the retina and exert a therapeutic effect.

Gaudreault taught specifically that "penetration of ranibizumab into the retina is critical for its clinical use" and that ranibizumab's "ability [to penetrate the retina] has been attributed to the small molecule size" of ranibizumab. PTX-1839 at 2, 6; Tr. 2026:2-2028:24 (Trout). Furthermore, Gaudreault's teachings were consistent with the scientific literature, which taught that proteins larger than 77 kDa would not penetrate the retina. Tr. 2028:25-2031:3; PTX-576 at 8 (Ghate) (the retina's "internal limiting membrane" was "impermeable to . . . globular molecules > 70 kDa"); PTX-1842 at 1 (Jackson) ("The [retinal exclusion limit] in human tissue was 76.5 ± 1.5 kDa."); PTX-1757 (Daly) ¶ 48 (the smaller 46 kDa "mini-trap" had "optimized characteristics for local/intra-vitreal delivery" and "has the ability to penetrate through the inner-limiting membrane (ILM) in the eye, and diffuse through the vitreous to the retina/retinal pigment epithelial (RPE) layer which will help to treat retinal disease").

As for Fraser, that reference undisputedly provides no teachings regarding intravitreal use of VEGF Trap and thus provides no motivation either. Because it was known that the protein later known as aflibercept had a molecular weight of 115 kDa,

substantially greater than the retinal exclusion limit, the POSA would not have been motivated to use aflibercept in an ophthalmic formulation. The overwhelming weight of the evidence thus demonstrated that the POSA would not have been motivated to combine Fraser and Lucentis with a reasonable expectation of success to achieve the claimed compositions, which require the specific aflibercept protein that is also glycosylated in an ophthalmic formulation. Adidas, 963 F.3d at 1359; see St. Jude Med., LLC v. Synders Heart Valve LLC, 977 F.3d 1232, 1242-43 (Fed. Cir. 2020).

d) The combination fails to teach multiple claimed limitations

Claim 1 – aflibercept amino acid sequence and glycosylation requirement

The combination of Fraser and Lucentis fails to teach several limitations of the claims. Neither Fraser nor the Lucentis publications teach the specific claimed amino acid sequence, i.e., amino acids 27-457 of SEQ ID NO:4. Nor did the Defendants advance any persuasive reason to select that sequence from among the several others known in the prior art. Tr. 2018:7-2022:16 (Trout); PTX-3619A. The combination's failure to teach these limitations weighs strongly against obviousness.

Dr. Rabinow relied on inherency for the glycosylation limitation, but failed to provide any evidence that aflibercept is necessarily glycosylated. Tr. 1044:13-19. As the Federal Circuit

has explained, "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." PAR Pharm., Inc. v. TWI Pharm., Inc., 773 F.3d 1186, 1194 (Fed. Cir. 2014) (quoting In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981) (emphasis added). The prior art provides numerous examples of nonglycosylated proteins, such as ranibizumab, DTX-726 at 31:34, and nonglycosylated fusion proteins, such as mini-Trap, PTX-1757 (Daly) ¶ 48. Furthermore, Dr. Trout explained that even if a protein contains amino acid sequences that may be glycosylated, a given protein may not be glycosylated. Tr. 2023:9-2025:23. Dr. Trout's testimony was supported by the scientific literature, see PTX-1773 (Sinclair) at 2, and Dr. Rabinow did not offer any contrary testimony. Thus, the Defendants failed to meet the "high standard" for proving inherency. PAR, 773 F.3d at 1195-96.

Nor did the Defendants provide any reason to make the claimed fusion protein glycosylated. The Defendants, as "a party seeking to invalidate a patent as obvious[,] must demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention." Cyclobenzaprine, 676 F.3d at 1068-69. The Defendants did not meet that burden. Dr. Rabinow did not advance

any motivation to glycosylate aflibercept. Dr. Trout explained that the POSA would have sought to use nonglycosylated aflibercept, because glycosylation increases size and thus decreases retinal penetration. Tr. 2022:20-2023:2, 2028:16-24, 2035:3-2036:24. Dr. Rabinow did not dispute this testimony and did not establish any affirmative reason why the POSA would want to increase molecular size via glycosylation.

Claim 1 — 98% native conformation

Each of the asserted claims requires that "at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography." The Defendants bear the burden not only of showing a motivation to combine the references to achieve the claimed invention, but also of "a reasonable expectation of success" in achieving the claimed invention. Endo Pharm. Inc. v. Actavis LLC, 922 F.3d 1365, 1377-78 (Fed. Cir. 2019). The Court finds that the Defendants have not shown a reasonable expectation of success in achieving the 98% native conformation limitation. The Defendants' argument is based on Dr. Rabinow's unsupported theory that formulations in a clinical trial would have 98% native conformation as claimed. The Court finds that the Defendants' assertion is unsupported by the prior art and that the Defendants

did not meet their burden in showing a reasonable expectation of success.

Nonetheless, even if all formulations in a clinical trial, such as the formulation disclosed in Shams, did have 98% native confirmation, Dr. Rabinow agreed that "[j]ust because one protein has a given native conformation at a specific condition, the [POSA] wouldn't expect that a different protein will have the same native conformation at that condition." Tr. 1156:20-24. The higher required concentration of aflibercept compared to the ranibizumab in Shams and aflibercept's identity as a fusion protein undermine any reasonable expectation of success. It was undisputed at trial that higher protein concentrations increase the risk for instability, and the claimed concentration of aflibercept (40 mg/ml) is four times higher than the 10 mg/ml concentration of ranibizumab in Shams. Tr. 2049:21-2050:21 (Trout); PTX-1556 (Wang 2005) at 7, 9. Thus, the Court finds that the POSA would not have had a reasonable expectation that the claimed formulations would have 98% native conformation in view of the Lucentis publications.

Furthermore, Dr. Trout explained that because fusion proteins are synthetic "Frankenstein" molecules that, unlike antibodies, did not evolve to possess inherent stability, the POSA would expect fusion proteins like aflibercept to have lower stability than antibodies (or antibody fragments like ranibizumab). Tr. 2068:18-

2069:7. Dr. Trout's explanation draws support in the scientific literature, PTX-1835 (Fast) at 15; Tr. 2014:21-2015:16 (Trout), and Dr. Rabinow did not offer any rebuttal. The Court thus finds that the Defendants did not demonstrate a reasonable expectation of success. Endo, 922 F.3d at 1377-78.

Claim 4 – polysorbate 20 concentration

Claim 4 of the Product Patent requires that "said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." The references in the Defendants' combination disclose three different concentrations of polysorbate 20: Fraser, a preclinical investigation of how intravenous administration of a VEGF Trap molecule affects ovarian function in monkeys, describes 0.1% polysorbate 20, DTX-729 at 2; Gaudreault, a preclinical study of intravitreal ranibizumab disclosed a composition with 0.05% polysorbate 20, PTX-1839 at 2; and Shams, directed to a clinical trial of ranibizumab, disclosed 0.01% polysorbate 20, DTX-726 at 31:27-32.

Despite offering testimony that more clinically advanced formulations would be more stable, Tr. 1031:7-16, Dr. Rabinow's conclusion of obviousness appears to assume that the POSA would not seek to use the 0.01% polysorbate 20 concentration in Shams, but rather would use the concentration from Fraser or Gaudreault. Dr. Rabinow did not offer any reason in the prior art's teachings

to prefer the polysorbate 20 concentration of Fraser or Gaudreault over the polysorbate 20 concentration contemplated for clinical use in Shams.

Dr. Trout, in contrast, considered Shams' teaching alongside Fraser and Gaudreault, and testified that if the POSA were to choose a polysorbate 20 concentration based on these references, the POSA would select the concentration in Shams, which is outside the scope of Claim 4, because it was the most clinically advanced. Tr. 2046:18-2047:13, 2048:5-2049:9. In view of the prior art's teachings and the trial record, the Court finds that the POSA would not have been motivated to select the polysorbate 20 concentration in Fraser or Gaudreault. Dr. Rabinow's approach is emblematic of hindsight, which is not permitted in the obviousness analysis. Sanofi-Aventis, 933 F.3d at 1375 (rejecting attempt to "chart[] a path to the claimed compound by hindsight").

Claim 9—pH

Claim 1 of the Product Patent, PTX-2, recites "a buffer," and claim 9 recites "wherein said buffer comprises a pH about 6.2-6.3." As with the polysorbate 20 concentration, the Defendants' prior art combination teaches three different pH values: 6.0 in Fraser, DTX-729 at 2; 5.0 in Gaudreault, PTX-1839 at 2; and 5.5 in Shams, DTX-726, 31:27-32. Dr. Trout gave unrebutted testimony that neither Gaudreault's 5.0 or Sham's 5.5 taught to use a pH of

"about 6.2-6.3." Tr. 2052:4-8. Dr. Rabinow, in contrast, did not establish any motivation to select the pH from Fraser, the only pH that arguably would fall within the claimed range. The Court thus concludes that the Defendants did not meet their burden to use a pH of "about 6.2-6.3" as required by claim 9.

For the reasons discussed, the Court concludes that the Defendants have failed to establish that the combination of Fraser and Lucentis render the Product Patent obvious.

iii. Fraser and Liu

a) The POSA would not have been motivated to combine Fraser and Liu

The Court holds that the Defendants did not establish a motivation to combine Fraser and Liu. The Defendants argue that Fraser, a study on the effect of VEGF Trap on ovarian function in monkeys, used a VEGF antagonist concentration (24.3 mg/ml) higher than Lucentis (6 or 10 mg/ml), so the POSA would consult Liu to "optimize" Fraser's formulation. Even if the evidence supported this leap, neither reference provides any motivation to use aflibercept intravitreally. As Dr. Trout explained, the POSA would not have turned to Fraser's study on ovarian function using intravenous administration of a VEGF Trap and combined it with Liu's disclosure, which addresses the viscosity of certain antibody formulations and "doesn't have anything to do with

aflibercept or anything related," to make the claimed ophthalmic formulations of aflibercept. Tr. 2060:23-2061:2, 2062:20-25; see Adidas, 963 F.3d at 1359 ("Fundamental differences between the references are central to this motivation to combine inquiry.").

Even if the POSA did consider Liu's teachings in making an intravitreal formulation, the Court finds that the POSA would have heeded Liu's teachings regarding viscosity and used a lower concentration of protein. Liu taught that "[a]ntibodies tend to form viscous solutions at high concentration" and that sugars can further increase viscosity. DTX-730 ¶ 6. Dr. Trout, along with Dr. Furfine and Dr. Graham, explained that high viscosity would be especially problematic for intravitreal injections because it leads to "very long injection times" and even can make the formulation unusable, which would be exacerbated by the high amount of sugar already in Fraser's formulation. Tr. 2066:2-21 (Trout); see also Tr. 573:3-8 (Furfine); Tr. 1687:23-1688:21 (Graham). Thus, Liu would not have motivated the POSA to increase Fraser's VEGF Trap concentration, because such increase would increase viscosity, which would have been particularly problematic for a formulation for intravitreal injection. See Henny Penny Corp. v. Frymaster LLC, 938 F.3d 1324, 1331-32 (Fed. Cir. 2019) (the cited prior art "must be considered for all its teachings, not selectively."). Dr. Rabinow did not address Liu's viscosity

teachings. Dr. Trout's and the inventors' unrebutted testimony, which are consistent with Liu's express teachings, weigh strongly against a lack of motivation to combine. Imperium, 757 F. App'x at 978-79; Raytheon, 993 F.3d at 1382.

The Defendants invoke precedent directed to overlapping ranges to meet the 40 mg/ml limitation, but neither reference discloses the relevant range pertinent to the claims, i.e., aflibercept concentration. The overlapping range cases may be invoked "when the only difference from the prior art is a difference in the range or value of a particular variable." In re Kumar, 418 F.3d 1361, 1366 (Fed. Cir. 2005). Where, as here, the prior art ranges have nothing to do with the "particular variable" claimed (aflibercept concentration), and instead are directed to different range—i.e., Liu's concentrations of completely different proteins with no relevance to VEGF, DTX-730 ¶¶ 279-80; Tr. 2065:7-22—the range law is inapposite. Pharmacyclics LLC v. Alvogen, Inc., 2022 WL 16943006, at *9 (Fed. Cir. Nov. 15, 2022) (not applying range law where "there are additional differences between the prior art and [the claim]"); Teva Pharm. v. Corcept Therapeutics, 18 F.4th 1377, 1382-83 (Fed. Cir. 2021) (range law did not apply where POSA would not expect claimed value and prior art range to behave same way); ModernaTx v. Arbutus Biopharma, 18 F.4th 1364, 1374 (Fed. Cir. 2021). Regardless, even if applicable,

any presumption of obviousness based on optimizing within a range is rebutted by "teaching away, unexpected results, or other pertinent evidence of nonobviousness." DuPont v. Synvina C.V., 904 F.3d 996, 1006 (Fed. Cir. 2018); Allergan, 796 F.3d at 1305 (concluding presumption was rebutted by teaching away and unexpected results). Gaudreault's teaching away and the other objective evidence of nonobviousness (discussed below) rebut any presumption here.

b) Fraser and Liu do not teach multiple claim limitations

As described above regarding the Fraser and Lucentis combination, Fraser does not teach the aflibercept sequence or its glycosylation. And Liu is undisputedly not directed to VEGF antagonists and does not disclose any sequences of such proteins, including aflibercept. Tr. 1151:22-24 (Rabinow); Tr. 2063:1-18 (Trout). The combination's failure to teach these claimed limitations weighs strongly against obviousness.

The Defendants rely on Liu for the 98% native conformation limitation, but Liu did not teach that formulations of aflibercept (or any other fusion proteins) would have 98% native conformation. Dr. Rabinow acknowledged that Liu described antibodies, not fusion proteins, and did not disclose any stability data for aflibercept or any other VEGF antagonist. Tr. 1152:20-1154:23 (Rabinow).

Crucially, both sides' experts agreed that "different proteins have different propensities for aggregation." Tr. 1155:25-1156:2 (Rabinow); Tr. 2068:5-2069:7 (Trout). Dr. Rabinow agreed that "[j]ust because one protein has a given native conformation at a specific condition, the [POSA] wouldn't expect that a different protein will have the same native conformation at that condition." Tr. 1156:20-24. And Dr. Trout explained, without rebuttal, that the POSA would have expected fusion proteins like aflibercept to be less stable than antibodies, since fusion proteins are "Frankenstein molecule[s]" that did not evolve like antibodies to possess inherent stability. Tr. 2068:18-2069:7; see PTX-1835 (Fast) at 15 ("fusion proteins may lack" the natural "interdomain interactions" that have "evolved to provide mutual stabilization"); Tr. 2014:21-2015:16, 2015:11-16 (Trout). In view of this evidence, which the Court credits, the Court finds that the Defendants failed to demonstrate the requisite reasonable expectation of success. Endo, 922 F.3d at 1373.

For the reasons discussed, the Court concludes that the Defendants have failed to establish that the combination of Fraser and Liu render the Product Patent obvious.

iv. Dix

The parties spend significant portions of their post-trial filings disputing the proper priority date of the Product Patent and, in turn, whether Dix '226 qualifies as a prior art reference. But the Court need not resolve these issues to get to the heart of the matter. For the reasons that follow, the Court finds that even if Dix '226 is prior art, it does not render the Product Patent obvious.

Dix '226 fails to render obvious the asserted claims for reasons similar to those explained above in connection with the Court's analysis of anticipation in light of Dix '226. Dix '226 undisputedly did not disclose, suggest, or contemplate ophthalmic formulations or intravitreal injections. Tr. 2072:18-20 (Trout); Tr. 1124:9-11, 1125:7-16 (Rabinow). Although Dix disclosed the range of 10-50 mg/ml of a VEGF antagonist, it disclosed no 40 mg/ml formulation, did not teach to use 40 mg/ml of the specific protein claimed, and provided no guidance as to whether any formulations in that range would be preferable for intravitreal use. DTX-13, 2:20-30. As discussed above, the Court finds that the 40 mg/ml "pre-lyophilized solution" was not an ophthalmic formulation or intended for injection, but rather was a "manufacturing intermediate" that the POSA would not have been motivated to use or have any expectation of success with regard to the 98% native

conformation limitation. Tr. 2077:1-16 (Trout). Furthermore, the Court's findings regarding objective evidence apply equally to the Defendants' obviousness case over Dix '226. Gaudreault undisputedly taught away from using a 40 mg/ml ophthalmic formulation, as described above, and the POSA would thus have been discouraged from using the 40 mg/ml concentration claimed in the Product Patent and would instead have used a lower concentration within the Dix '226 range. Tr. 2072:25-2073:18 (Trout).

Thus, the Defendants have failed to establish that Dix '226 alone renders the asserted claims obvious.

v. Objective Evidence of Nonobviousness

At trial, Regeneron presented objective evidence of nonobviousness relevant to the Product Patent: teaching away, unexpected results, industry skepticism, and copying. Objective evidence "may often be the most probative and cogent evidence in the record," Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983), as it "guard[s] against slipping into use of hindsight" and "the temptation to read into the prior art the teachings of the invention at issue," Apple, 839 F.3d at 1052 (quoting Graham, 383 U.S. at 36). Here, the objective evidence strongly supports nonobviousness.

Along with refuting the requisite motivation, AstraZeneca v. Mylan, 19 F.4th at 1335, evidence of teaching away constitutes objective evidence of nonobviousness. Ecolochem, Inc. v. S. Cal. Edison Co., 227 F.3d 1361, 1379 (Fed. Cir. 2000) (considering teaching away as objective evidence); Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998) (same). As described above, the prior art taught away from using a 40 mg/ml concentration of a VEGF antagonist.

Unexpected properties are present where "the claimed invention exhibits some superior property or advantage" that a POSA "would have found surprising or unexpected." Procter & Gamble, 566 F.3d at 994. Here, the unexpected properties of the claimed 40 mg/ml aflibercept compositions compared to the "closest prior art," the 40 mg/ml ranibizumab formulation in Gaudreault, strongly support nonobviousness. Millennium, 862 F.3d at 1368. The Defendants did not dispute that Gaudreault's 40 mg/ml formulation was the closest prior art.

The Court finds that Eylea's unexpected properties are well supported in the scientific literature.[7] Eylea is undisputedly an

[7] At trial, Dr. Rabinow testified that Eylea's properties were not unexpected because it was known that certain VEGF Trap molecules had strong binding affinity for VEGF. Tr. 1093:1-25. The Defendants forfeited this argument by not citing or discussing it in their Opening Post-Trial Brief. See Vanda Pharms., Inc. v. Teva Pharms. USA, Inc., 2022 WL 17593282, at *12 n.1 (D. Del. Dec.

embodiment of the claims, as it contains 40 mg/ml of glycosylated aflibercept, a buffer (pshosphate), a stabilizing agent (sucrose), 0.03% polysorbate 20, and meets the 98% native conformation limitation. PTX-2, 9:20-44 (example 3); Tr. 2083:8-25 (Trout). The Court finds that Eylea demonstrated three critical and unexpected properties: comparable (1) safety and (2) efficacy to ranibizumab, along with (3) the durability to be dosed half as frequently as ranibizumab (after three loading doses for wet AMD). PTX-1155 (Thomas) at 4. Extended dosing with Eylea was not only unexpected, but revolutionary, providing "immediate benefits to patients who have a difficult time with intravitreal dosage administration" for the first time. Id. The "captivating aspect" of aflibercept that made "bimonthly dosing" possible and "altered current regimens of monthly dosing" was its "extended half-life." Id.; Tr. 2083:8-25, 2085:11-2086:5 (Trout). In contrast, the 40 mg/ml Gaudreault formulation led to "moderate to severe" inflammation, no increase in VEGF inhibition over 10 mg/ml, and was ultimately discarded. The Court finds that these "captivating" properties, which enabled a major change in the treatment of

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13, 2022), aff'd, 2023 WL 3335538 (Fed. Cir. May 10, 2023) (holding that a party "forfeited its right" to raise a specific argument "by not raising it in timely fashion" and "by the passing manner in which it raised the argument in its post-trial brief"). Even if not forfeited, the Court would not credit Dr. Rabinow's testimony.

ophthalmic disease, were a "difference in kind" and not merely degree as compared to the 40 mg/ml Gaudreault formulation, Allergan, 796 F.3d at 1307.

The Defendants contest whether there is an adequate "nexus" between Eylea's unexpected properties and the claimed invention. However, the Court finds that Regeneron established a sufficient nexus between the claims and the unexpected properties. Here, "there is a presumption of nexus for objective [evidence]" because Regeneron showed undisputedly "that the asserted objective evidence is tied to a specific product," i.e., Eylea, "and that product is the invention disclosed and claimed in the patent." WBIP, 829 F.3d at 1330 (quotation marks omitted); see Crocs, 598 F.3d at 1311 ("Because the Commission found, based on substantial evidence, that Crocs shoes practice the '858 patent and that the Crocs shoes were commercially successful, Crocs established a prima facie case of nexus."). As relevant here, "the patent owner can show that it is the claimed combination as a whole that serves as a nexus for the objective evidence." WBIP, 829 F.3d at 1330. That is what Regeneron did. The record at trial demonstrated that the unexpected properties stemmed from the claimed compositions as a whole, including the 40 mg/ml aflibercept concentration. As the Defendants stress, and all appear to agree, the aflibercept protein does contribute to the longer half-life of Eylea, PTX-1155 at 4,

but aflibercept's concentration is also critical to its half-life. As Dr. Furfine explained, a key insight of the inventors was that "every time you double the concentration that you inject, you get an extra half-life." Tr. 473:2-15; see In re Sullivan, 498 F.3d at 1352 (considering inventor testimony regarding unexpected properties and holding that Board erred by not considering inventor declaration). Dr. Furfine's testimony explaining the relationship between the concentration and the half-life was unrebutted. Only with the higher 40 mg/ml concentration, resulting in a 2 mg dose, did Regeneron even attempt a bimonthly dosing regimen, as the trial record demonstrated unequivocally. PTX-1155 at 4, Table 1; Tr. 125:2-126:16, 135:7-23 (Yancopoulos). Dr. Trout likewise explained that the stability of the claimed compositions, including the required 98% native conformation, indicated to the POSA that the "there's a relatively lower risk of inflammation." Tr. 2170:5-21. Thus, Regeneron demonstrated a nexus between the unexpected properties and the claimed compositions, none of which were disclosed in the prior art.

The Defendants criticize the Product Patent for not describing Eylea's clinical and pharmacokinetic properties. However, the law does not require the inventors to have appreciated that the Eylea composition they invented would become the success it is; "understanding of the full range of an invention is not

always achieved at the time of filing the patent application," and unexpected properties need not be appreciated at the time of the invention. Knoll Pharm. Co. v. Teva Pharm. USA, Inc., 367 F.3d 1381, 1384-85 (Fed. Cir. 2004); Genetics Inst., 655 F.3d at 1307-08 ("[W]e have held that evidence of unexpected results may be used to rebut a case of *prima facie* obviousness even if that evidence was obtained after the patent's filing or issue date." (emphasis added) (collecting cases)). The claimed compositions could have been among the many clinical failures Regeneron had experienced during its decades of existence. Tr. 97:16-98:7 (Yancopoulos). But Eylea was not one of them. The claimed composition — 40 mg/ml of aflibercept, with polysorbate 20, a buffer, and a stabilizing agent — instead became the leading medicine in its class and a revolutionary treatment for treating angiogenic eye disorders. Tr. 1745:3-1746:16 (Graham); Tr. 151:16-24 (Yancopoulos). Those results support nonobviousness.

Regeneron also pointed to evidence of industry skepticism, which may also support nonobviousness. WBIP, 829 F.3d at 1335 ("If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness. Doubt or disbelief by skilled artisans regarding the likely success of a combination or solution weighs against the notion that one would combine elements

in references to achieve the claimed invention."). Dr. Trout pointed to the teachings of Ferrara 2004 (PTX-1838), which taught the POSA that clinical use of fusion proteins like aflibercept "remains to be validated" and suggested that the "junctions between the various structural elements in such multi-component molecules can generate an immune response." PTX-1838 at 7. Dr. Trout explained that the POSA would have heeded the warning of Ferrara 2004, which was cited over 3,000 times by other authors. Tr. 2080:4-2081:19 (Trout). Specifically, Dr. Trout explained, "as a formulator," that the possibility of an immune response "is foremost in our mind of concern or one of the things that are of foremost concern." Id. Dr. Rabinow did not dispute the teachings of Ferrara 2004. The skepticism of Ferrara 2004—directed specifically at the use of VEGF Trap fusion protein and expressing "[d]oubt . . . by skilled artisans regarding the likely success of a combination or solution," WBIP, 829 F.3d at 1335—supports nonobviousness.

Dr. Trout also considered another Ferrara reference, Ferrara 2006 (PTX-701), and offered testimony that Ferrara 2006 constituted industry skepticism of the claimed invention. Tr. 2081:9-19. For the reasons expressed above with respect to teaching away, the Court finds that the teachings of Ferrara 2006 constitute further evidence of industry skepticism specifically

directed at intravitreal compositions comprising high molecular weight proteins such as VEGF Trap fusion proteins, and further support nonobviousness. PTX-701 at 4; WBIP, 829 F.3d at 1335.

Evidence of copying can also support nonobviousness, and has greater force when the infringer tries but fails to circumvent the claimed invention. Depuy Spine v. Medtronic, 567 F.3d 1314, 1328-29 (Fed. Cir. 2009). Regeneron presented evidence that the [redacted] The Defendants' copying of these aspects of the Eylea formulation supports nonobviousness. Depuy, 567 F.3d at 1328-29. [redacted]

[redacted] still weighs in favor of nonobviousness. Copying requires only "substantial similarity" with the patented product, not identicality. Medtronic, Inc. v. Teleflex Innovations S.a.r.l., 70 F.4th 1331, 1340–41 (Fed. Cir. 2023).

Having considered the Defendants' asserted prior art combinations and all of the evidence, in addition to Regeneron's arguments and objective evidence of nonobviousness, the Court concludes that the Defendants have failed to prove by clear and convincing evidence that the asserted claims of the Product Patent would have been obvious.

c. The Product Patent is not invalid under § 112

The Defendants raise three challenges under 35 U.S.C. § 112 against the claims of the Product Patent. First, the Defendants assert that the term "suitable for intravitreal administration" recited in claim 1 is invalid as indefinite. Second, the Defendants assert that the claims of the Product Patent lack written description, focusing largely on claim 1. Third, the Defendants assert that the claims of the Product Patent are not enabled, also focusing on claim 1's limitations. Having reviewed the Defendants' arguments and Plaintiff's responses at trial, the

Court concludes that the Defendants have not met their burden of proving invalidity under § 112 for any claim of the Product Patent, either claim 1 on which they focus or the narrower dependent claims asserted at trial.

i. The Asserted Claims are not Indefinite.

Indefiniteness requires clear and convincing evidence to prove that the POSA could not understand with "reasonable certainty" what "suitable for intravitreal administration" means in the claims, despite the disclosure in the specification and the term's common use in the field. Nautilus Inc. v. Biosig Instruments, Inc., 572 U.S. 898, 901 (2014); see BASF, 875 F.3d at 1365 (indefiniteness assesses claim language "when read in light of the specification"). Courts have evaluated the claim term "suitable"—including in contexts similar to this one—and repeatedly concluded that this term is not indefinite. See, e.g., Dey, L.P. v. Teva Parenteral Medicines, Inc., 2011 WL 2461888, at *3-7 (N.D.W. Va. June 17, 2011) (finding claim term "suitable for direct administration" not indefinite), aff'd, 600 F. App'x 773 (Fed. Cir. 2015); Talecris Biotherapeutics, Inc. v. Baxter Int'l Inc., 510 F. Supp. 2d 356, 361 (D. Del. 2007) (finding claim term "suitable for intravenous administration" not indefinite); UCB, Inc. v. Accord Healthcare, Inc., 201 F. Supp. 3d 491, 545 (D. Del.

2016), aff'd, 890 F.3d 1313 (Fed. Cir. 2018) (finding claim term "suitable" not indefinite because the "record [was] devoid of any evidence that a POSA would need 'clear guidelines' or 'explicit guidance' or 'the upper and lower limits'" to understand the term); In re Watson, 517 F.2d 465, 477 (C.C.P.A. 1975) (finding claim term "suitable" not indefinite); Panasonic Corp. v. Magna Int'l Inc., 2022 WL 625089, at *19 (W.D. Tex. Mar. 3, 2022) (same); Tecnomatic S.p.A v. ATOP S.p.A., 2021 WL 1410036, at *19 (E.D. Mich. Feb. 23, 2021), report and recommendation adopted , 2021 WL 2309933 (E.D. Mich. June 7, 2021) (same); Copan Italia S.p.A. v. Puritan Med. Prod. Co. LLC, 2019 WL 5699078, at *8 (D. Me. Nov. 4, 2019) (same); Sherwin-Williams Co. v. PPG Indus., Inc., 2018 WL 3845239, at *7 (W.D. Pa. Aug. 13, 2018) (same); Phoenix Licensing, L.L.C. v. AAA Life Ins. Co., 2015 WL 3866832, at *7 (E.D. Tex. June 22, 2015) (same); A.L.M. Holding Co. v. Akzo Nobel Surface Chemistry LLC, 2014 WL 12927041, at *3 n.19 (D. Del. Nov. 5, 2014) (same).

Both parties offered testimony demonstrating that the POSA understood the scope of the asserted claims, including the term "suitable for intravitreal administration." Dr. Rabinow had no difficulty opining which formulations were "suitable for intravitreal administration" in asserting obviousness. Tr. 1171:3-19 (Rabinow). And Dr. MacMichael conceded that knowledge

about "what formulations would be suitable for intravitreal administration" was "available in the literature," then agreed that the POSA could also consult an ophthalmologist—although Dr. MacMichael did not do so despite opining that the term is indefinite. Tr. 1519:7-18 (MacMichael). Dr. MacMichael's criticism was not that the scope of the claims was unclear, but rather that the claims were "open-ended and broad." Tr. 1520:3-1521:6.

The testimony from both parties confirmed that the POSA would not have viewed the term "suitable for intravitreal administration" as subjective. Dr. Trout testified that "suitable for intravitreal injection" is not subjective; the POSA would assess suitability by looking "to the teachings of the patent," which describe exemplary excipients, see PTX-2 at 4; and then, if needed, looking at "the literature" for suitable excipients with "structures that had been used in intravitreal administration" and consulting an ophthalmologist. Tr. 2112:20-2113:7 (Trout). Unlike Dr. MacMichael, who cited no evidence in support of his opinion, Dr. Trout cited literature as to how the POSA would interpret "suitable for intravitreal administration" — literature illustrating that those of skill in the art use and understand this term. Tr. 2114:5-2115:23 (citing Chang, PTX-1832 at 16 ("[I]t is preferred to select excipients that have been used in marketed

products with a relevant route of delivery."); Peyman, PTX-1758, 3:26 at 4 (using the similar term "suitable for the treatment of ocular neovascularization").

The Defendants strain to find ambiguity where none exists—as their own experts' testimony demonstrates. Tr. 1171:3-19; BASF Corp. v. Johnson Matthey Inc., 875 F.3d 1360, 1368 (Fed. Cir. 2017) (expert's repeated use of terms "implicitly confirms that the terms at issue are ones whose scope is understood with reasonable certainty" by POSA); Sonix Tech. v. Publ'ns Int'l, 844 F.3d 1370, 1378-79 (Fed. Cir. 2017) (term not indefinite where expert has "no difficulty in applying it"). And Dr. MacMichael conceded that knowledge about "what formulations would be suitable for intravitreal administration" was "available in the literature," then agreed that the POSA could also consult an ophthalmologist — which Dr. MacMichael never did, despite opining that the term is indefinite. Tr. 1519:7-18. Dr. MacMichael's criticism was not that the scope of the claims was unclear, but rather that the claims were "open-ended and broad." Tr. 1520:3-1521:6. But as the Federal Circuit and its predecessor court have confirmed repeatedly, "breadth is not indefiniteness." BASF, 875 F.3d at 1367; SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1341 (Fed. Cir. 2005); In re Gardner, 427 F.2d 786, 788 (C.C.P.A. 1970).

The Defendants' attempted reliance on Dr. Furfine's testimony is misplaced. See Defs.' Opening Br. 28. The testimony they cite was directed to what was known "[b]efore [his] patent," i.e., without its guidance, whereas the indefiniteness analysis considers the meaning of a claim term in view of the patent's specification. Tr. 544:4-12 (Furfine). The Court also disagrees with the Defendants' suggestion that Dr. Trout's opinions were inconsistent. See Defs.' Opening Br. 29. Dr. Trout explained that the prior art did teach excipients suitable for intravitreal injection. Tr. 2114:5-2115:23. That does not imply, however, that the POSA would expect, based on the prior art without the patent's disclosure and data, to succeed in obtaining a stable, 40 mg/ml formulation of aflibercept with 98% native conformation as claimed in the Product Patent.

Supported only by Dr. MacMichael's conclusory opinion, the Defendants argue that "suitable for intravitreal administration" is "subjective." Tr. 1417:9-15, Defs.' Opening Br. 28. But the term bears no resemblance to subjective claim terms like "aesthetically pleasing," which turn entirely on "the preferences of the particular user." Interval Licensing LLC v. AOL, Inc., 766 F.3d 1364, 1371 (Fed. Cir. 2014); Defs.' Opening Br. 28. The Defendants identified no circumstances where skilled artisans would disagree whether a formulation was "suitable for

intravitreal injection" based on their subjective preferences. See, e.g., Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1346, 1350 (Fed. Cir. 2005) (terms indefinite where they depend solely on individuals' "subjective beliefs"); Intellectual Ventures v. T-Mobile USA, 902 F.3d 1372, 1381 (Fed. Cir. 2018) (claims indefinite if they depend on "the unpredictable vagaries of any one person's opinion"); NuVasive, Inc. v. Alphatec Holdings, Inc., 557 F. Supp. 3d 1069, 1076 (S.D. Cal. 2021) (finding claim term indefinite where the patentee's expert "could only offer an opinion for himself" about the precise boundaries of the claim term and "did not feel he could comment for other[s]"); Cypress Lake Software, Inc. v. Samsung Elecs. Am., Inc., 382 F. Supp. 3d 586, 610 (E.D. Tex. 2019) (finding claim term indefinite where the patentee's expert conceded that "[d]ifferent people will have different interpretations" of the claim term's boundaries); Prolifiq Software Inc. v. Veeva Sys. Inc., 2014 WL 3870016, at *7 (N.D. Cal. Aug. 6, 2014) (in finding claim term indefinite, posing questions regarding claim boundaries and concluding that "[s]ome people would say yes to these questions, some would say no.").

Dr. Trout testified that "suitable for intravitreal injection" is not subjective; the POSA would assess suitability by looking "to the teachings of the patent," which describe exemplary excipients, PTX-2, at 4 (2:39-48); and then, if needed, looking at

"the literature" for suitable excipients with "structures that had been used in intravitreal administration" and consulting an ophthalmologist. Tr. 2112:20-2113:7. Unlike Dr. MacMichael, Dr. Trout cited literature as to how the POSA would interpret the term. See Tr. 2114:5-2115:23 (Trout) (citing Chang, PTX-1832 at 6 ("[I]t is preferred to select excipients that have been used in marketed products with a relevant route of delivery"); Peyman, PTX-1758 at 4 (using term "suitable for the treatment of ocular neovascularization")). The Court thus concludes that the term "suitable for intravitreal injection" meets the standard for definiteness, which does not require "absolute or mathematical precision." See Biosig Instruments v. Nautilus, 783 F.3d 1374, 1381 (Fed. Cir. 2015); see Presidio Components v. Am. Tech. Ceramics, 875 F.3d 1369, 1376 (Fed. Cir. 2017) (claims definite where POSA would know "general approach" to ascertain whether claim term was met).

The Defendants have therefore failed to establish that the Product Patent is invalid under § 112 as indefinite.

ii. The Asserted Claims Do Not Lack Written Description

A patent satisfies the written description requirement if the specification "allows [the POSA] to visualize or recognize the identity of the subject matter purportedly described"; the patent need not contain "either examples or an actual reduction to practice." Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1308 (Fed. Cir. 2015). Further, the written description requirement does not require that the specification "describe in the specification every conceivable and possible future embodiment of [the] invention." Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003) (internal quotation omitted). Although the patent need not provide examples or demonstrate reduction to practice, the patent specification here provides both—including multiple formulations with different combinations of excipients and corresponding stability data (PTX-2 at 7-8 (Examples 1-6)) and lists of suitable excipients and amounts (PTX-2 at 4 (2:39-48)). Because the claims are drawn to a specific protein at a specific concentration with specific concentration ranges of polysorbate 20, the Court holds that the specification allows the POSA "to visualize or recognize the identity of the subject matter purportedly described" and thus meets the written description requirement. See Allergan, 796 F.3d at 1308.

Dr. Trout testified that each of the claim limitations in the Product Patent have "common structural features," including the "very specific" VEGF antagonist and the categories of organic co-solvent, buffer, and stabilizing agent. Tr. 2109:17-2110:3 (Trout). He further testified that these structures were well known in the art. Tr. 2110:1-5. Dr. MacMichael did not dispute this assertion, acknowledging that buffers and stabilizing agents are both "a known set of structures." Tr. 1509:13-1510:9, 1511:14-23 (MacMichael). Dr. MacMichael even identified the handful of buffers that the POSA would consider in a formulation. Tr. 1494:6-25 (MacMichael).

Dr. Trout also testified that the POSA could recognize the formulations that were claimed in the Product Patent, could visualize the formulations within the claims, and could recognize from the specification that the inventors invented the claimed formulations. Tr. 2110:11-19 (Trout). As for the specific disclosures in the Product Patent that allowed the POSA to recognize these features, Dr. Trout pointed to the disclosure of column 2, lines 39 to 57, as well as each of the examples. Tr. 2110:20-25 (Trout); see also Tr. 2100:7-2104:20 (discussing disclosures in detail). Those disclosures conveyed what structures would fall within the scope of the claim, permitting the POSA to visualize the claimed formulations and to recognize

that the inventors invented and possessed what the Product Patent claims. Tr. 2100:7-2104:19, 2110:20-25 (Trout). He noted that all of the Product Patent's examples have "at least 98 percent native conformation as measured by SEC after two months," and all "meet the turbidity limitation of Claim 15." Tr. 2111:4-9 (Trout).

Following this analysis, Dr. Trout testified that the Product Patent provided "species or examples representative of the genus," claimed structures rather than function, and thus provided adequate written description for the asserted claims. Tr. 2111:1-21 (Trout). The Court credits Dr. Trout's analysis and conclusion.

The Defendants criticize the claims for reciting the structural categories of "buffer" and "stabilizing agent" instead of specific chemical structures. But Dr. MacMichael acknowledged that buffers were "a known set of structures," Tr. 1509:13-1510:9, as were stabilizing agents, Tr. 1511:14-21, and he readily identified the handful of buffers that the POSA would consider in a formulation, Tr. 1494:6-25. The POSA therefore can "visualize or recognize" the claimed structures. Dr. Trout agreed that buffers and stabilizing agents were "structures well known in the art." Tr. 2110:1-5. For such known classes of structures, the patent did not need to provide an exhaustive description to the POSA. McRO, Inc. v. Bandai Namco Games Am. Inc., 959 F.3d 1091, 1100 (Fed. Cir. 2020) (A "patent need not teach, and preferably

omits, what is well known in the art." (quoting Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534 (Fed. Cir. 1987)); Erfindergemeinschaft UroPep GBR v. Eli Lilly & Co., 276 F. Supp. 3d 629, 650 (E.D. Tex. 2017) (Bryson, J.) (patent did not need to describe "hundreds of" compounds already "known" and within the claims to satisfy written description), aff'd, 739 F. App'x 643 (Fed. Cir. 2018). Rather, patents may describe such known structures through a "generalized formula" just as they may describe more specific chemical structures. In re Driscoll, 562 F.2d 1245, 1250 (C.C.P.A. 1977).

Further, a patent may satisfy the written description requirement by describing "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." Ariad, 598 F.3d at 1350. Since the specification here identifies the common structural features of the claimed compositions—40 mg/ml aflibercept, polysorbate 20, a buffer, and a stabilizing agent—and provides multiple examples thereof, it satisfies the written description requirement. Alcon Rsch. v. Barr Labs., 745 F.3d 1180, 1190-91 (Fed. Cir. 2014). The claims did not need to exclude other embodiments to comport with § 112; "[i]t is not the function of claims to exclude . . . but to point out what the combination is." In re Anderson, 471 F.2d 1237, 1242 (C.C.P.A. 1973).

****SEALED****

MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

The Court has considered the decision in AstraZeneca AB v. Mylan Pharm. Inc., 2022 WL 16857400 (N.D.W. Va. Nov. 9, 2022), which has since been vacated, No. 18-cv-193, ECF No. 625 (N.D.W. Va. Mar. 8, 2023) ("AstraZeneca v. Mylan 2022"). While the decision is not binding, the Court finds that the factual record in that case is inapposite to the one here. The AstraZeneca court found that although "the asserted claims contain common structural limitations[,] . . . there is no correlation between such limitations and the functional stability requirement." 2022 WL 16857400, at *21. That was because the evidence in that case showed the "POSA could not apply [the] information [in the specification] to predict stable formulations" outside the examples as the structures "interact in interrelated and unpredictable ways." Id. at *13, 21 n.14.

Here, in contrast, the evidence demonstrated that the examples in the specification were predictive of the performance of formulations that were not exemplified in the patent. Regeneron pointed to several working examples of embodiments that were outside the disclosed examples (and the prior art) but nonetheless met the 98% native conformation and turbidity limitations of the claims. Tr. 1729:11-1732:3 (Graham) (discussing PTX-2281 and PTX-2282, showing a formulation using mannitol instead of sucrose as a stabilizing agent, that met both limitations); 1732:4-1733:23

(Graham) (discussing PTX-2265, PTX-2266, and PTX-2267, showing a formulation with 0.06% polysorbate 20 that likewise met both the 98% native conformation and turbidity limitations). The Defendants did not dispute these results, nor did the Defendants point to any formulation within the claims that did not achieve the claimed functional properties. Thus, unlike in AstraZeneca, here there was a "correlation between structure and function" that informs the POSA which formulations possess the properties recited in the claims. 2022 WL 16857400, at *21; see Ariad, 598 F.3d at 1350 ("correlation between structure and function" may satisfy written description requirement). Unlike in Ariad and its progeny, which involved claims to unlimited classes of molecules defined only by function, 598 F.3d at 1356; AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1292 (Fed. Cir. 2014) ("The claims . . . at issue in these appeals define the claimed antibodies by their function."), here the claims are limited to a specific protein molecule at a specific concentration along with other known structures (a buffer, stabilizing agent, and polysorbate 20). Just as in Alcon, the patent's description of those compositions shows possession of the claimed invention and thus satisfies the written description requirement, notwithstanding that "various formulation parameters, including osmolality and pH" may be selected when practicing the invention

(although notably, claim 9 does specify the pH as well). See 745 F.3d at 1191.

Furthermore, in contrast to the evidence in AstraZeneca v. Mylan 2022 that the structures "interact in interrelated and unpredictable ways," 2022 WL 16857400, at *13, the evidence showed that the POSA would have pursued a more linear process that, the Defendants' expert agreed, would not require making and testing each permutation of the structural elements of the claim, and that the POSA could use formulation design systems. For example, the Kaisheva reference (DTX-3610) instructs that "[t]he formulation development approach is as follows: selecting the optimum solution pH, selecting buffer type and concentration, evaluating the effect of various excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients using an I-optimal experimental design." DTX-3610 ¶ 54. Consistent with Kaisheva's teachings, Dr. MacMichael and Dr. Trout agreed that the POSA would not need to make and test every possible formulation in order to practice the claims. Tr. 1497:25-1499:9 (MacMichael) (explaining that by using available software packages, "design of experiments" or "DOE" "reduces the amount of work," and "scientists would know that a DOE can be used to effectively reduce the number of variables that have to be looked at in an actual physical wet chemistry lab"); Tr. 2106:19-2108:4 (Trout) (agreeing that a POSA

would use experimental design methods to reduce amount of experimentation).

Thus, the Court concludes that the Defendants have failed to demonstrate by clear and convincing evidence that the asserted claims of the Product Patent are invalid for lack of written description.

iii. The Asserted Claims Do Not Lack Enablement

The Supreme Court recently explained that although "a specification may call for a reasonable amount of experimentation to make and use a patented invention," it may not leave the POSA "forced to engage in 'painstaking experimentation' to see what works." Amgen Inc. v. Sanofi, 143 S. Ct. 1243, 1255-56 (2023). The Supreme Court's reasoning is consistent with the Federal Circuit's longstanding rubric inquiring whether making and using the claimed invention calls for "undue experimentation." Wands, 858 F.3d at 736-37.

During his testimony, Dr. Trout applied each of the Wands factors to the asserted claims of the Product Patent, supporting his conclusion that the claims are enabled because practicing the full scope of the claims requires only "routine experimentation," not "undue experimentation." Tr. 2109:6-14 (Trout).

Dr. Trout first testified about the breadth of the claims, Wands factor 8. He stated that the asserted claims are "narrow" rather than broad, because they claim "one specific biologic molecule . . . with a specific sequence ID" at just one concentration (40 mg/m), in a vial for intravitreal administration, and further claim specific structural components including a buffer, stabilizing agent, and the organic co-solvent of polysorbate 20 within a "narrow range." Tr. 2089:10-2090:4 (Trout). He also explained that the claim limitation reciting "98 percent present in native conformation following storage at 5 degrees Celsius for two months as measured by size-exclusion chromatography" is a narrowing limitation that removes suspensions and emulsions from the scope of the claims. Tr. 2090:16-24 (Trout). The Court finds that this factor weighs in favor of enablement.

Regarding the nature of the invention, Wands factor 4, Dr. Trout testified that "the nature of the invention is . . . an ophthalmic formulation . . . suitable for intravitreal administration, with the various formulation components, including the aflibercept and with the 98 percent native after two months storage at 5 degrees Celsius and all the rest of the specifics." Tr. 2091:16-24. The experts agreed that the patent does not disclose or claim novel ingredients and does not require using or

inventing novel ingredients to practice. See Tr. 1493:2-10 (MacMichael); Tr. 2125:15-20 (Trout). The Court finds that this factor weighs in favor of enablement.

Regarding the relative level of skill of the POSA, Wands factor 6, Dr. Trout testified that the level of skill was high—that is, the POSA "would be a professional with a master's degree at least in a relevant field, so a technical field directly relevant to formulations here." Tr. 2092:6-17 (Trout). Dr. MacMichael testified that the POSA would have an even higher level of skill: "at least a PhD in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins or a lower degree with more practical industrial experience." Tr. 1372:25-1373:14 (MacMichael). The Court finds that this factor weighs in favor of enablement.

Regarding the level of predictability of the art, Wands factor 7, Dr. MacMichael notably did not testify that experimentation practicing the full scope of the claims would be unpredictable. He did not identify any formulation with the claimed components that failed to meet the 98% native conformation limitation, and Dr. Trout testified that he was not aware of any such formulation, either, see Tr. 2091:25-2092:5 (Trout).

Further, in responding to Dr. MacMichael's reliance on materials suggesting that developing a stable formulation was nonroutine or not straightforward, Dr. Trout testified that those materials were inapposite, in that they did not disclose aflibercept formulations, whereas the Product Patent itself taught how to make stable aflibercept formulations. Tr. 2092:25-2096:3 (Trout). The Court finds that this factor weighs in favor of enablement.

Regarding the specification's guidance and working examples, Wands factor 2, Dr. Trout testified as to the "significant guidance" in the Product Patent. See Tr. 2096:4-22 (Trout). In particular, Dr. Trout highlighted the patent's disclosure of "known structures" as the claimed components, including an organic cosolvent such as polysorbate, polyethylene glycol, propylene glycol, or a combination thereof; a buffer such as phosphate and other known buffers that would achieve the disclosed pH range, such as succinate or histidine buffer; a stabilizing agent such as sucrose, sorbitol, glycerol, trehalose, or mannitol; and a pH range of 6.2 to 6.3. Tr. 2096:7-2099:18 (Trout). He also explained that "given the various formulations in the examples, if one encompasses the various structures that are described in the claims, one expects to meet the 98 percent limitation, or again the 99 under some circumstances with the different times." Tr. 2100:2-6 (Trout). Dr. Trout provided further testimony explaining

specifically the relevance of guidance in Example 1, Tr. 2100:7-2103:18; Example 3, 2103:19-2014:7; and Example 5, 2104:8-2105:4. He also testified that Examples 4 and 6, which are "similar" to Examples 3 and 5 except that "they're in prefilled syringes instead of vials," are "important for a general understanding of how these formulations work too." Tr. 2105:5-17. As for the lyophilized formulations in Examples 7 and 8, Dr. Trout stated that lyophilization is just "another way of making formulations" taught by the specification. Tr. 2090:5-13. He testified that this Wands factor thus favored enablement. Tr. 2105:22-2106:1. The Court agrees and finds that this factor weighs in favor of enablement.

Regarding the state of the prior art, Wands factor 5, Dr. Trout testified that this factor weighed in favor of enablement because the prior art taught "how to substitute one excipient in a category, such as a stabilizing agent or buffer, for another," in addition to teaching how to perform SEC and turbidity testing. Tr. 2106:2-15 (Trout). The Court finds that this factor weighs in favor of enablement.

Regarding quantity of experimentation, Wands factor 1, Dr. Trout testified that the steps of formulation development—which the Defendants' experts had called a "design of experiments" approach—involve "selecting optimal solution pH, selecting buffer type, concentration of the buffer, evaluating the effect of various

excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients." Tr. 2106:23-2107:9 (Trout); see also DTX-3610 (Kaisheva) ¶ 54. Based on this approach, Dr. Trout testified that the POSA would not need to test every possible combination of buffers and stabilizing agents in practicing this claim," but would instead "test the various combinations and variations of those combinations as the '865 patent did and via experimental design as needed." Tr. 2107:10-14 (Trout). The POSA would know to "use excipients that have the same structures, same structural characteristics as those discussed in the various categories in the patent," Tr. 2107:20-2108:4, further reducing the quantity of experimentation needed to practice the claims. Dr. MacMichael similarly testified that "the POSA could do a design of experiment" using available computer software to "show which variables are not getting you to the desired outcome," which "reduces the amount of work" needed to practice the claims. Tr. 1497:1-1499:12 (MacMichael). The Court thus finds that it was not necessary to make and test every formulation within the claims in order to determine whether it would meet the 98% native conformation or turbidity limitations. The Court finds that this factor weighs in favor of enablement.

Likewise, the Court finds that the scope of the claims is not directed substantially to inoperative embodiments. Each of the

Product Patent's several examples meets both the 98% native conformation and the turbidity limitation. And Regeneron pointed to several examples of embodiments that were outside the disclosed examples (and the prior art) but nonetheless met the 98% native conformation and turbidity limitations of the claims. Tr. 1729:11-1732:3 (Graham) (discussing PTX-2281 and PTX-2282, showing a formulation using mannitol instead of sucrose as a stabilizing agent, that met both limitations); 1732:4-1733:23 (Graham) (discussing PTX-2265, PTX-2266, and PTX-2267, showing a formulation with 0.06% polysorbate 20 that likewise met both the 98% native conformation and turbidity limitations). The Defendants did not dispute these results, nor did the Defendants point to any formulation within the claims that would require undue experimentation to make and use (when guided by the patent's teachings) or that did not exhibit the claimed properties.

Dr. Trout applied each of the Wands factors in turn and offered credible testimony concluding that practicing the asserted claims required only routine and not undue experimentation. Tr. 2089:7-2109:14 (Trout); see Wands, 858 F.2d at 737. Critically, "it is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." Johns Hopkins, 152 F.3d at 1360. Here, however, the Defendants' experts

repeatedly declined to support that undue experimentation would be necessary to practice the claims, let alone prove nonenablement by clear and convincing evidence. While Dr. MacMichael also analyzed the asserted claims under these Wands factors, he repeatedly declined to offer the opinion that practicing the claims would require experimentation that rose to the level of "undue"—the longstanding requirement for non-enablement. See Tr. 1483:17-1487:13, 1535:3-1536:12 (MacMichael). The Defendants' other expert, Dr. Rabinow, agreed with Dr. Trout regarding enablement: "it wouldn't require undue experimentation to make formulations falling within the scope of the asserted claims." Tr. 1168:1-4 (Rabinow). The Court credits Dr. Trout's (largely unrebutted) testimony and finds the asserted claims enabled.

The claims recite specific structures, and the specification provides significant guidance to practice the claims, with examples and lists of excipients and amounts to use, as Dr. Trout explained. Tr. 2088:23-2106:1 (Trout). Using this guidance and tools for automating formulation design, Tr. 2106:19-2108:4 (Trout), Tr. 1497:1-1499:12 (MacMichael), DTX-3610 (Kaisheva) ¶ 54, the POSA could practice the claims with minimal and routine—not undue—experimentation, Tr. 2109:6-14 (Trout). "Such routine experimentation does not constitute undue experimentation"—"a considerable amount of experimentation is permissible, if it is

merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention." Johns Hopkins, 152 F.3d at 1360 (quoting PPG, 75 F.3d at 1564); Wands, 858 F.2d at 736-40.

The Defendants argue that the claims cannot be both nonobvious and enabled and accuse Dr. Trout of inconsistency. The Court disagrees. Dr. Trout correctly applied the legal standards: obviousness is determined "in view of the prior art" without the benefit of the specification, whereas enablement is assessed "after reading the specification"; as a result, "there is no tension" in finding claims both nonobvious and enabled. See Allergan, 796 F.3d at 1310. The Defendants' articulation would collapse obviousness and enablement into two sides of the same inquiry as if the patent specification's teachings did not exist—that is not the law.

The Court likewise does not find persuasive the Defendants' citation to Regeneron's statements made during prosecution. As Dr. Trout explained, Dr. Dix was not addressing, in prosecution, experimentation in view of the Product Patent's teachings. Rather, Dr. Dix addressed, with respect to obviousness of a different patent, that "arriving at a stable formulation is not a

straightforward matter and it is not, for instance, possible to apply a formulation for one drug to another." Tr. 2094:7-2095:3; DTX-4430 at 3-4. Again, what matters for the enablement inquiry is what experimentation would be necessary "after reading the specification," Allergan, 796 F.3d at 1310, and at that point the POSA would not be left with applying formulations from one drug to another because the patent describes how to formulate aflibercept—the molecule in the claims—with numerous examples and additional disclosures. Tr. 2095:3-2096:3.

The Court also concludes that AstraZeneca v. Mylan 2022 does not support the Defendants' nonenablement arguments. 2022 WL 16857400 (N.D. W.Va. Nov. 9, 2022). While the decision is not binding on this Court, the Court nonetheless concludes that the factual record in that case is inapposite to the one here, for reasons similar to those above. In the AstraZeneca v. Mylan 2022 case at issue, the evidence showed that "[d]ue to the unpredictability of the art and lack of prior art to inform a POSA about the interactions between the ingredients, a POSA would have to test an astronomical number of formulations." 2022 WL 16857400, at *7. That was because the formulation ingredients "interact in interrelated and unpredictable ways." Id. at *13. That fatal aspect of practicing the claims in AstraZeneca was also the same as in the Federal Circuit's Idenix case, the Supreme Court's Amgen

case, and the Federal Circuit's similar precedent: those cases premised their findings of non-enablement explicitly on the need for the POSA to make and test each compound or structure within structurally unlimited claims to determine whether it would work. Amgen, 143 S. Ct. at 1257 (specification "leave[s] [POSA] to 'random trial-and-error discovery'"); Idenix Pharm. LLC v. Gilead Sci. Inc., 941 F.3d 1149, 1161 (Fed. Cir. 2019) (POSA had to "make[] and test[]" "each" of unlimited set of structures); Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380, 1384-85 (Fed. Cir. 2013) (claims purported to cover "any structural analog" of compound, and POSA could evaluate claimed function only by "synthesizing and screening each" compound); Pharm. Res., Inc. v. Roxane Labs., Inc., 253 F. App'x 26, 30 (Fed. Cir. 2007) ("a large part of the asserted claims' scope is directed toward inoperative embodiments," and experiments "evidence[d] numerous unsuccessful attempts . . . to practice subject matter within the scope of the claims").

Unlike in each of those cases, there is no such evidence of interactions among the various ingredients, necessitating making and testing an "astronomical" number of formulations at random, for the formulations claimed here. The evidence showed that the POSA would have pursued a more linear process that would not require making and testing each permutation of the structural

elements of the claim, and that would have been aided by formulation design systems. For example, the Kaisheva reference (DTX-3610) instructs that "[t]he formulation development approach is as follows: selecting the optimum solution pH, selecting buffer type and concentration, evaluating the effect of various excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients using an I-optimal experimental design." DTX-3610, ¶ 54. Consistent with Kaisheva's teachings, Dr. MacMichael and Dr. Trout agreed that the POSA would not need to make and test every possible formulation in order to practice the claims. Tr. 1497:25-1499:9 (MacMichael) (explaining that by using available software packages, "design of experiments" or "DOE" "reduces the amount of work," and "scientists would know that a DOE can be used to effectively reduce the number of variables that have to be looked at in an actual physical wet chemistry lab"); Tr. 2106:19-2108:4 (Trout) (agreeing that POSA would use experimental design methods to reduce amount of experimentation).

Furthermore, the AstraZeneca v. Mylan 2022 court found that making "embodiments outside the scope of the disclosed examples would require substantial trial-and-error testing." 2022 WL 16857400, at *17. Here, however, the Defendants have not pointed to any experimentation that would be necessary to make and test

formulations outside the claims. Because the Defendants "failed to make the threshold showing that any experimentation is necessary to practice the [claims]," their enablement arguments fail. Alcon, 745 F.3d at 1189; see McRO, Inc. v. Bandai Namco Games Am. Inc., 959 F.3d 1091, 1100 (Fed. Cir. 2020) (Defendants generally must make "concrete identification of at least some embodiment or embodiments asserted to be not enabled" so that claim "breadth is shown concretely and not just as an abstract possibility.").

In contrast, Regeneron pointed to several examples of embodiments that were outside the disclosed examples (and the prior art) but nonetheless met the 98% native conformation and turbidity limitations of the claims. Tr. 1729:11-1732:3 (Graham) (discussing PTX-2281 and PTX-2282, showing a formulation using mannitol instead of sucrose as a stabilizing agent, that met both limitations); 1732:4-1733:23 (Graham) (discussing PTX-2265, PTX-2266, and PTX-2267, showing a formulation with 0.06% polysorbate 20 that likewise met both the 98% native conformation and turbidity limitations). The Defendants did not dispute these results, nor did the Defendants point to any formulation within the claims that would require undue experimentation to make and use (when guided by the patent's teachings) or that did not exhibit the claimed properties. Again, the Defendants thus failed to make a threshold

showing of nonenablement. Alcon, 745 F.3d at 1189; McRO, 959 F.3d at 1100.

Similarly, the Defendants have not argued, let alone proven, that identifying formulations having the claimed structure (40 mg/ml of glycosylated aflibercept and polysorbate 20 within the specified concentration range, plus a buffer and a stabilizing agent) that exhibit the claimed properties amounts to finding a "needle in a haystack" using trial-and-error experimentation with a significant number of failures. AstraZeneca v. Mylan 2022, 2022 WL 16857400, at *19 (discussing Idenix, 941 F.3d at 1162); Roxane, 253 F. App'x at 30. Unlike the "needle in a haystack" problem in Idenix, the experimental process here of identifying formulations having the claimed properties would be more akin to finding hay in a haystack. Each of the examples in the Product Patent achieved both the 98% native conformation and the turbidity limitation. PTX-2, Examples 1-8. And again, the Defendants did not point to any example of a formulation with the claimed structures that would not exhibit the claimed properties, whereas Dr. Graham pointed (without rebuttal) to multiple formulations outside the specification's examples, but within the claims, that meet the claimed properties. Alcon, 745 F.3d at 1189.

The Court also concludes that the Supreme Court's recent decision in Amgen Inc. v. Sanofi, 143 S. Ct. 1243 (2023) is readily

distinguishable. There, the claims were entirely functionally defined—the Court explained that the patentee "seeks to monopolize an entire class of things defined by their function—every antibody that both binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors." 143 S. Ct. at 1256. Here, in contrast, the claims are directed to formulations of a specific protein at a specific concentration—not "an entire kingdom" of proteins. The excipients recited in the claims are also structures: categories for the buffer and stabilizing agent, and a specific substance (polysorbate 20) for the organic co-solvent. Because the claims in Amgen were not limited to any particular structure, the POSA was left with "painstaking experimentation to see what works," id. at 1256-57 (quotation marks omitted), since "changing even one amino acid in the sequence can alter an antibody's structure and function," id. at 1249. For such claims, limited specifications "offer[] [the POSA] little more than advice to engage in 'trial and error,'" and "the public does not receive its benefit of the bargain." Id. at 1257-58. Those challenges associated with altering protein structure are irrelevant to practicing the claims here, which are limited to a particular amino acid sequence of aflibercept. Cf. id. at 1250 (noting that patents claiming a particular amino acid sequence were not at issue). As described above, the Defendants did not

present any evidence or argument that varying the claimed excipient structures (all known in the art) would have engendered the kind of "painstaking experimentation" necessary in Amgen. Id. at 1256-57.

Thus, the Court concludes that the Defendants have failed to demonstrate by clear and convincing evidence that the asserted claims of the Product Patent are invalid for lack of enablement.

4. Invalidity of the Treatment Patents

i. Dixon Does Not Anticipate Claim 6

The Defendants cite Dixon (DTX-204) as an anticipating reference. It is undisputed that Dixon does not expressly discuss the concept of isotonicity, and thus fails to disclose expressly "all of the limitations claimed" and "all of the limitations arranged or combined in the same way as recited in the claim." Net MoneyIN, 545 F.3d at 1371. Instead, the Defendants argue that Dixon inherently anticipates Claim 6 on the ground that "the missing descriptive material is necessarily present, not merely probably or possibly present, in the prior art." Trintec, 295 F.3d at 1295. They that Dixon's reference to "VEGF Trap-Eye" as "formulated with different buffers and at different concentrations (for buffers in common) suitable for the comfortable, non-irritating, direct injection into the eye," only could have been

describing an isotonic solution. DTX-204 at 3. In support of this position, the Defendants' clinical expert, Dr. Albini, relied on testimony offered by the Defendants' formulation expert, Dr. Rabinow, as to what the POSA would have believed about this sentence. See Tr. 828:12-830:17 (Albini); Tr. 1098:23-1100:7 (Rabinow); DTX-204 at 3.

There is insufficient evidence that the "isotonic" limitation of claim 6 is necessarily present in Dixon's reference to formulations "suitable for the comfortable, non-irritating, direct injection into the eye." DTX-204 at 3.

The Defendants' expert Dr. Rabinow did not rule out that a comfortable, non-irritating injection could be something other than isotonic. He testified that "[t]he eye is remarkably tolerant to hypertonic solutions" exceeding the range of osmolality or tonicity for isotonic solutions, Tr. 1174:6-8 (Rabinow), showing that even he recognizes that formulation of aflibercept for a "comfortable, non-irritating injection" need not necessarily be isotonic. Evidence that a comfortable, non-irritating injection *might* be isotonic is not enough to meet the Defendants' burden to show inherent anticipation, which "may not be established by probabilities or possibilities." Continental, 948 F.2d at 1269.

Dr. Rabinow's testimony on this issue lacked credibility, including because he failed to explain the scientific basis for

his opinions. Dr. Albini's testimony — whether on his own behalf or by reliance on Dr. Rabinow — cannot fill this gap, because Dr. Albini admitted that he has no opinion regarding what "range outside of isotonicity you would or wouldn't use to treat the eye." Tr. 881:19-22 (Albini). To the extent Dr. Albini purported to offer testimony without reliance on Dr. Rabinow about what the language in Dixon would have been understood to mean from a formulation perspective, the Court declines to credit it. Dr. Albini admitted he is "not a formulation expert," and is "not an expert" in "the design of therapeutics" or "the importance of the isotonicity." Tr. 819:2-16, 823:9-14 (Albini). He has "no" opinion regarding "what specific range outside of isotonicity you would or wouldn't use to treat the eye." Tr. 881:19-22 (Albini). He acknowledged he was "definitely relying on" Dr. Rabinow for any opinion on formulation issues, Tr. 913:17-914:6 (Albini), including whether "aflibercept formulated for comfortable, non-irritating injection was inherently isotonic," Tr. 942:2-12 (Albini).

Indeed, although the Defendants' expert, Dr. Rabinow, initially maintained that a POSA would not have viewed a hypertonic formulation as suitable for intravitreal administration, Tr. 1171:3-7 (Rabinow), when he was confronted by his prior statements during cross-examination, Tr. 1171:9-19, he agreed that "[t]he eye

is remarkably tolerant to hypertonic solutions," Tr. 1173:6-1174:8 (Rabinow), supporting the conclusion that an injection may be "comfortable and non-irritating" to the eye, yet not isotonic.

The Defendants argue that Regeneron did not identify at trial "an isotonic aflibercept formulation" in use "that was not comfortable, and that did irritate the eye," and therefore "Dixon anticipates." ECF No. 576 (Defs.' Opening Post-Trial Brief) at 10-11. This not only impermissibly flips the burden of proof onto Regeneron to cite an example, but it also seeks the wrong type of example. As a factual matter, the question is not whether there existed some irritating isotonic aflibercept formulations; the question is whether Dixon's disclosure of a "comfortable and non-irritating" solution teaches that the aflibercept formulation necessarily must be isotonic. The Court finds that Dixon did not necessarily describe an isotonic formulation, because there is evidence that ophthalmic formulations of aflibercept existed that were not isotonic, including the formulation disclosed in Example 5 of the Product Patent, which was hypotonic ("below iso-osmolar"). Tr. 1721:11-1722:8 (Graham). And there was no evidence that as of the priority date, the POSA would have had information about which of the formulations disclosed in the Product Patent—all described as "suitable for intravitreal administration," PTX-2 at 2—were isotonic, or which, if any, of the formulations it disclosed was

being developed and used in the clinical studies. See Tr. 1742:4-1743:2 (Graham).

The Court therefore does not credit Dr. Albini's ultimate conclusion that Dixon constitutes an anticipatory reference. While that alone constitutes a failure of proof, the Court also credits the testimony of Plaintiff's formulation expert Dr. Trout that the POSA would not have understood Dixon to say that aflibercept's formulation necessarily and only would be isotonic. Tr. 2117:6-24 (Trout).

The Court finds that the Defendants failed to demonstrate by clear and convincing evidence that all the limitations of claim 6 were disclosed in Dixon.

ii. Prior Art Renders Claim 6 Obvious

The Defendants have carried their burden, however, to demonstrate that claim 6 is rendered obvious by the combination of Dixon and Hecht.

The Defendants relied on the testimony of Dr. Albini and Dr. Rabinow in forming its obviousness arguments regarding claim 6 of the '572 patent. The Defendants rely, generally, on the same prior art disclosures of Dixon for their obviousness arguments as they did for anticipation. For example, Dr. Albini testified that Dixon disclosed the claimed dosing regimen through its disclosure of 2.0

mg VEGF Trap-Eye administered "at an 8 week dosing interval (following three monthly doses)." (Tr. 812:12-813:3 (Albini); DTX 204.4).

Dr. Albini also deferred to the expert background and testimony of Dr. Rabinow and his analysis of the Chemistry section of Dixon and the isotonic formulation limitation of claim 6. (See, e.g., Tr. 813:7-14, 819:5-8, 826:7-23, 914:1-6 (Albini); DTX 204.3). This disclosure alone, based on what Dr. Albini learned from Dr. Rabinow, suggested to Dr. Albini that the formulation described in Dixon should be isotonic. (Tr. 828:12-19 (Albini)).

However, Dr. Rabinow also testified that claim 6 of the '572 patent as construed by this Court is obvious in view of the disclosures from the Dixon reference. (Tr. 1096:15-21 (Rabinow)). For example, Dr. Rabinow explained that a POSA reading Dixon would understand that the phrase "suitable for the comfortable, non-irritating direct injection into the eye" in Dixon would tell a POSA that the formulation should be isotonic. (Tr. 1098:9-1099:10 (Rabinow)).

Dr. Rabinow further relied upon the Hecht reference, (Tr. 1096:23-1097:8 (Rabinow); see generally DTX 3588), which is an excerpt from Remington's Pharmaceutical Sciences, a reference that the asserted patents admit is a "formulary known to all pharmaceutical chemists" and contains "a multitude of appropriate

formulations." (PTX 1.13 (5:55-58); PTX 3.16 (5:64-6:1). Hecht disclosed that ophthalmic solutions like aflibercept are formulated to be "sterile, isotonic, and buffered for stability and comfort," and that for such formulations, "isotonicity always is desirable and particularly is important." (Tr. 1097:9-22 (Rabinow); DTX 3588.11, 13). Dr. Rabinow explained that Hecht stresses that tonicity is a "general consideration" that formulators must consider when formulating an ophthalmic solution. (Tr. 1097:23-8 (Rabinow); DTX 3588.11, 13).

Dr. Rabinow likened these disclosures in Hecht to the disclosures of Dixon; notably, he stated that Hecht's ophthalmic solution guidance was particularly relevant to the disclosure in Dixon describing the aflibercept solution as "formulated with different buffers and at different concentrations for buffers in common suitable for the comfortable, nonirritating direct injection into the eye." (Tr. 1098:11-1099:4 (Rabinow); DTX 204.3). Dr. Rabinow explained that this disclosure, given the guidance gleaned from Hecht, would signal to a POSA that the aflibercept formulation described in Dixon should be isotonic. (Tr. 1099:5-22 (Rabinow)).

As with anticipation, Regeneron presented the testimony of Dr. Csaky and Dr. Trout to rebut the Defendants' arguments. Dr. Csaky testified that Dixon does not expressly disclose an isotonic

formulation, and that any disclosure from Dixon would not be helpful to an ophthalmologist because they are not trained chemists. (Tr. 1868:8-1869:6 (Csaky)). Dr. Csaky also testified that the POSA would not have known the formulation of Eylea as of the date of Regeneron's Phase 3 trials and the filing date of the dosing patents, nor could a POSA such as Dr. Albini or Dr. Csaky offer an opinion as to what range would qualify as outside the isotonicity limitation. (Tr. 1869:11-13 (Csaky); see also Tr. 881:19-22, 913:17-25 (Albini)). On cross-examination of Dr. Albini, he admitted that the full formulation for Eylea had not been disclosed to the public in an identifiable prior art reference; however, Dr. Csaky did confirm that the isotonicity formulation component had been available as of November 2010. (Tr. 915:17-20 (Albini); Tr. 1979:12-1981:1 (Csaky); DTX 917.1-2; DTX 918.1). Dr. Csaky further deferred to Dr. Trout, (Tr. 1956:17-19 (Csaky)), who also testified that no prior art reference disclosed the aflibercept isotonic formulation limitation. (Tr. 2117:6-15 (Trout)).

With regard to Claim 6 the parties do not dispute that Dixon discloses the regimen. The Court also agrees with the Defendants that the claimed isotonic solutions were obvious in view of the disclosures of Dixon and Hecht, as explained by Dr. Albini and Dr. Rabinow.

The record further shows that a POSA would have had a reasonable expectation of success at using the claimed regimens. First, the record shows that there already were regimens in the prior art that permitted 5 monthly injections followed by less frequent administration. (See, e.g., DTX 2035.2-3; DTX 2730.22; DTX 3198.2). With regard to claim 6, the record reflects that the VIEW Phase 3 regimen, which Regeneron does not dispute falls within the scope of claim 1, was disclosed in the prior art Dixon reference, among other references, and that the Phase 2 results, using an even less aggressive dosing strategy than the Phase 3 regimen, resulted in significant improvement in visual acuity. (See DTX 204.4).

Second, "[a] finding of a reasonable expectation of success does not require absolute predictability of success" at making the invention. Almirall, LLC v. Amneal Pharms. LLC, 28 F.4th 265, 275 (Fed. Cir. 2022); see also OSI Pharms., LLC v. Apotex Inc., 939 F.3d 1375, 1385 (Fed. Cir. 2019) (declining to hold that "data is always required for a reasonable expectation of success" or to require "absolute predictability of success"). Dr. Csaky admitted that the claimed regimens showed some efficacy. (Tr. 1822:23-1823:17 (Csaky)); see Hoffmann-La Roche Inc. v. Apotex Inc., 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness."). Dr. Csaky also admitted

that aflibercept exhibited visual acuity gains in AMD using an even less aggressive dosing schedule than the Phase 3 schedule. (Tr. 1881:14-1882:20 (Csaky) (CLEAR-IT 2 had less loading doses and different design than VIEW trials); Tr. 1882:24-1883:7 (Csaky) (CLEAR-IT 2 clearly showed "activity" in terms of "effect on visual acuity"); Tr. 1974:25-1977:2 (Csaky) (positive results from CLEAR-IT 2); DTX 204.4-5). Under this standard, the Court finds that the Defendants have shown a POSA would have had a reasonable expectation of success at using the treatment regimen in claim 6. The Defendants' expert Dr. Albini testified as to several references that reported visual acuity gains (though no such gains are required of the claims), including aflibercept references showing efficacy in DME patients with just a single intravitreal injection or in the related AMD indication with repeated intravitreal injections. (Tr. 790:25-792:2 (Albini); DTX 3102.3 ("The median improvement in BCVA was nine letters at 1 month and three letters at 6 weeks. . ."); see also DTX 204.3-4). The record also reflects positive results obtained with the VEGF inhibitor ranibizumab in the treatment of both AMD and DME. (See, e.g., DTX 2733.1 (mean gain of eight (8) letters in DME); DTX 3089.1, 4 (8 of 10 eyes showed visual acuity gains in DME); see also, e.g., DTX 2034.1 (mean gain of 7.2 letters in AMD); DTX 3115.1 (mean visual

acuity improvement of 9.3 letters in AMD); DTX 4061.4 (various studies in AMD)).

Third, the Defendants have shown that the differences, if any, between the prior art and the claimed dosing regimen, do not rise to the level of being nonobvious. Regeneron has not presented any evidence of differences between the prior art dosing regimens and the claimed regimens.

The Court finds that the Defendants have demonstrated by clear and convincing evidence that claim 6 is obvious in light of Dixon and Hecht. Based on this conclusion, the Court does not address the Defendants' assertion that claim 6 is also invalid under § 112.

iii. Prior Art Does Not Anticipate the DME Claims

Claim 11 of the '601 patent provides: A method for treating diabetic macular edema in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months, "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly." PTX-1 at 21.

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MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

Claim 25 of the '572 patent provides: "A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient in a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept; wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose. The method of claim 15 wherein four secondary doses are administered to the patient." PTX-3 at 25.

Both claims are directed to methods of treating patients with diabetic macular edema, where the physician administers five loading doses of aflibercept at a 2 mg dosage level, approximately 4 weeks or one month apart, followed by maintenance or extended fixed interval dosing approximately every 8 weeks or two months apart for the remainder of treatment. While the claims do not use the phrase "loading doses," the parties' experts appeared to agree that this is the concept described in both claims. Tr. 297:24-299:17 (Csaky); Tr. 862:22-863:14 (Albini); Tr. 1287:10-14 (Stewart); Tr. 1332:7-10 (Stewart).

The Court finds that the Defendants failed to demonstrate by clear and convincing evidence that the method of claim 11 and claim 25 were disclosed by a single reference in the prior art. Neither of the two references the Defendants offered as anticipatory—a September 14, 2009 Press Release that describes aspects of Regeneron's Phase 2 DA VINCI trial (DTX-3198) and an earlier Regeneron patent referred to as the '747 patent (DTX-2730)—discloses every limitation of claims 11 and 25, as the law of anticipation requires.

a) September 14, 2009 Press Release

The Defendants urge that the September 14, 2009 Press Release Regeneron issued concerning several of its ongoing clinical trials anticipates claims 11 and 25. It does not. The relevant language from the Press Release provides:

> VEGF Trap-Eye is also in Phase 2 development for the treatment of Diabetic Macular Edema (DME). VEGF Trap-Eye dosed at 0.5 mg or 2 mg monthly, 2 mg every eight weeks after three monthly loading doses, or 2mg on an as-needed (PRN) basis after three monthly loading doses is being compared to focal laser treatment, the current standard of care in DME.

DTX-3198 at 2. This language describes regimens that contain three monthly loading doses, not five monthly loading doses, as the DME Claims require.

The Defendants to not assert that the September 2009 Press Release (DTX-3198) literally describes the claimed treatment

regimen. Plainly, it does not, because it discloses three loading doses (not the claimed five) followed by a PRN dosing schedule (not the claimed fixed eight-week interval). DTX-3198 at 2. As such, the Press Release does not disclose every element of the claimed method, let alone those elements as arranged in the claimed method. Net MoneyIN, 545 F.3d at 1369.

Instead, the Defendants argue that the POSA "would easily envisage" the claimed regimen as one possible regimen that could result from the administration of three loading doses followed by PRN treatment. They focus on the description of one arm of the Phase 2 DA VINCI trial where patients were being treated with 2.0 mg of aflibercept for 3 initial loading doses, followed by PRN treatment. They rely on Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356, 1361 (Fed. Cir. 2012), to argue this disclosure is anticipatory because the POSA "would easily envision the rest of the regimen to include one option with 5 doses, separated by 4 weeks, followed by an 8-week dose interval." ECF No. 576 at 14. In other words, the Defendants argue it is possible doctors following the regimen described in the Press Release would administer the three monthly loading doses described in the Press Release and then, for a given patient, just so happen to administer injections during the PRN phase in a pattern that matches that of the claimed regimen—(1) an injection at the first PRN visit, (2)

an injection at the second PRN visit, (3) no injection at the third PRN visit, and (4) an injection at the fourth PRN visit. The Defendants argue such a pattern of injections conforms to the claimed regimen because it equates to five monthly doses followed by a dose eight weeks later, as the asserted claims require.

The Court disagrees; Wrigley is inapposite. In Wrigley, a case about chewing gum containing a combination of WS-23 (a cooling agent) and menthol (a flavoring agent), the prior art reference "list[ed] several categories of components that can be included in the compositions." Wrigley, 683 F.3d at 1360. The Court held that the reference anticipated because it plainly "envision[ed] using WS-23 and menthol in a single product" and "the number of categories and components in [the] reference was [not] so large that the combination of WS-23 and menthol would not be immediately apparent to one of ordinary skill in the art." Id. at 1361. In other words, the limitations of the claims themselves were disclosed in the prior art reference. That logic does not apply to the September 2009 Press Release, which does not disclose five loading doses and does not disclose various regimen components in a manner it suggests can be mixed and matched; it rather discloses a single regimen—three monthly loading doses followed by PRN dosing—that is not the one claimed.

The evidence at trial did not support the Defendants' assumptions. Dr. Albini testified that this theory of anticipation assumes that the PRN regimen employed in the September 14, 2009, Press Release was a monthly PRN regimen. Tr. 918:20-23 (Albini). But the undisputed evidence at trial demonstrates that a "PRN" regimen need not be monthly—it can occur on other intervals, including once every two months, as was done, for example in the "READ 2" trial. Tr. 904:23-905:6 (Albini); PTX-3340. The September 2009 Press Release upon which the Defendants rely as prior art does not specify whether that trial's PRN dosing regimen was conducted monthly. Tr. 1865:3-15 (Csaky) (Press Release does not disclose "when those prn exams were being scheduled in this trial.").[8] In the absence of such a disclosure, the number of possible dosing permutations administered during the PRN phase is virtually infinite. There is no reason the POSA would "easily envisage" the claimed regimen from among them.

[8] The September 2009 Press Release does not disclose the details of the protocol actually used in Regeneron's study. Mylan did not suggest at trial that the DA VINCI study itself — or any other clinical study conducted by Regeneron — was itself prior art that could render the Asserted Treatment Claims invalid nor did it establish that any patient in that study received 5 loading doses followed by a dose eight weeks later, as the claimed regimen required."

The Defendants' own expert, Dr. Albini, acknowledged that there is no reason any particular patient would "necessarily" receive the claimed pattern of doses on the basis of the September 2009 Press Release's disclosure of an as-needed, PRN dosing phase. Tr. 919:4-14 (Albini) (agreeing that "[t]he Week 12 dose is one possibility from that [prn] dosing regimen, but it is not necessarily going to occur."). Regeneron's expert, Dr. Csaky, testified to the same effect. Tr. 1848:19-1849:25 (Csaky). In sum, the parties' experts agreed that if doctors performed the method described in the September 14, 2009 Press Release, it is merely *possible* that a patient would receive the claimed dosing regimen (among the many other possibilities), depending on the result of the examination the doctors performed in the study at each PRN visit, and whether that examination dictated that the patient should receive an injection. Tr. 1864:5-11 (Csaky) ("A prn is a conditional treatment, right? I wait, I see, I examine, take OCT."). That is insufficient to establish anticipation. Infra, ¶¶ 473-76.

Nor is this case analogous to In re Petering, 301 F.2d 676 (C.C.P.A. 1962), and its progeny, in which the court deemed the prior art anticipatory because it "expressly spelled out a definite and limited class of compounds that enabled a person of ordinary skill in the art to at once envisage each member of this limited

class," including those claimed, Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1376 (Fed. Cir. 2006) (describing holding of Petering). Here, by contrast, the number of potential patterns of injections that fall within the September 2009 Press Release's disclosure of three-monthly doses followed by PRN dosing on an undisclosed schedule is virtually limitless; the POSA would not "immediately envisage" every one of those possibilies, nor is there any narrower set of "preferred" regimens within the September 2009 Press Release's disclosure that would limit the inquiry. Accordingly, the September 2009 Press Release fails to meet the legal standard for anticipation.

In the absence of an express disclosure of the claimed invention, the Defendants' theory of anticipation is necessarily one of "inherent" anticipation. Net MoneyIN, 545 F.3d at 1371 (anticipatory reference must disclose expressly or inherently every element of claim as arranged in the claim). The Defendants' theory fails because it falls far short of the exacting standard for inherent anticipation—which requires that the undisclosed material is necessarily present in the disclosure—not merely possibly or probably present. Continental, 948 F.2d at 1269 ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); Therasense, Inc. v. Becton, Dickinson & Co., 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("Inherency,

however, may not be established by probabilities or possibilities."). Possibilities and probabilities are all the Defendants presented at trial.

First, the Defendants' theory of anticipation relies on the assumption that the PRN regimen employed in the September 14, 2009 Press Release was a monthly PRN regimen. But the Press Release does not specify the PRN interval, and undisputed evidence confirms other PRN intervals are possible and were indeed discussed at trial. Id. Because it is merely possible and not necessarily true that the PRN interval disclosed in the September 2009 press release involved monthly PRN, the Defendants failed to establish anticipation on the basis of the September 2009 Press Release. Trintec, 295 F.3d at 1295 ("Inherency . . . may not be established by probabilities or possibilities."); see also Continental, 948 F.2d at 1269; Therasense, 593 F.3d at 1332; Perricone v. Medicis Pharm. Corp., 432 F.3d 1368, 1376–79 (Fed. Cir. 2005) (narrow application of applying lotion to sunburned skin not inherently anticipated by broad application of applying lotion topically).

Furthermore, even if one were to assume, contrary to law and the Press Release's disclosure, that the PRN dosing described in the September 2009 Press Release was monthly PRN dosing, the Defendants' anticipation theory still depends on probabilities and possibilities. The PRN dosing phase would result in an overall

regimen of five monthly doses followed by an eight-week dosing interval only if for a given patient those examinations just so happened to result in the need to administer (1) a dose at the first PRN opportunity, (2) a dose at the second PRN opportunity, (3) no dose at the third PRN opportunity, and (4) a dose at the fourth PRN opportunity. And, again, this would only be the case if one were to assume the potential PRN dosing occurred monthly. No disclosure in the September 2009 Press Release makes this pattern of injections inevitable or necessarily true, and therefore it falls short of inherently anticipating the claims. Trintec, 295 F.3d at 1295; Continental, 948 F.2d at 1269; Therasense, 593 F.3d at 1332; Perricone, 432 F.3d at 1376-79.

Accordingly, the Court holds that the Defendants failed to establish by clear and convincing evidence that the September 2009 Press Release anticipates the DME Claims.

b) '747 Patent

Defendants also have asserted that U.S. Patent No. 7,303,747, assigned to Regeneron, anticipates claims 11 and 25. It is undisputed that the '747 patent does not expressly disclose a regimen of five loading doses followed by extended fixed dosing intervals; nor does it direct itself to the concept of loading doses followed by fixed extended dosing intervals. DTX-2730. The

Defendants principally rely on Example 17 of the '747 Patent for their anticipation theory, which — according to Dr. Albini — "describes an initial injection" that is "followed by subsequent treatments given within one- to six-month intervals." Tr. 785:17-23. But Example 17 is not directed to Diabetic Macular Edema (or Diabetic Retinopathy), as the claims require, but is instead titled (and directed to) "Age-Related Macular Degeneration." DTX-2730, 20:15-67. In response, the Defendants' expert Dr. Albini stated that the patent was generally directed to "angiogenic eye disorders," but did not explain why such a disclosure applied to Example 17 or rendered its teachings broader than its title of "Age-Related Macular Degeneration." Tr. 916:7-12 (Albini). Nor did Dr. Albini identify any disclosure of diabetic macular edema in the patent whatsoever. Id. Accordingly, the Court concludes that the '747 patent does not disclose every limitation of the DME claims, and the disparate disclosures from the '747 patent on which the Defendants rely are not arranged as they are in the DME claims.

Dr. Albini nevertheless testified that the POSA would "immediately envisage" from the '747 patent treating DME with a series of monthly doses that result from "continuous monitoring" of patients, followed by an eight-week gap (also the result of such monitoring). Tr. 785:24-786:22 (Albini). However, as with the September 2009 Press Release, this is a speculative outcome,

not one that "necessarily" would result from the methodologies described in the '747 patent. And despite Dr. Albini's testimony that the POSA would "immediately envisage" this scenario, his testimony on this point was undermined by the fact that he agreed at his deposition that the combinations of potential regimens contained in the '747 patent were "infinite," Tr. 236:8-12 (Albini), and that as to a more time limited period of administration, he had "not calculated the exact number of permutations possible." Tr. 917:7-15 (Albini).

The Court also credits Dr. Csaky's testimony that the methods of treatment that the '747 patent describes are directed to PRN regimens based on monitoring individual patients, Tr. 1861:20-1862:16 (Csaky), not fixed-interval dosing, and his unrebutted testimony that the language of the '747 patent does not provide any criteria that would inform the POSA as to what schedule a physician should use to treat the patient. Tr. 1862:17-25 (Csaky). Dr. Albini in fact agreed that the specification of the '747 patent pointed toward "the need for continuous monitoring of patients," Tr. 786:7-16 (Albini), which, as described above, is different than the fixed dosing schedule provided for by claims 11 and 25.

Turning next to the '747 patent, the Court holds that it also fails to anticipate the DME Claims for substantially the same reasons. Again, the parties agree that the '747 patent does not

expressly disclose a regimen for the treatment of DME using five monthly loading doses of aflibercept followed by a dose eight weeks later—instead it discloses an initial dose followed by subsequent doses one to six months later. Supra ¶¶ 215-16. It is undisputed that this disclosure encompasses an infinite number of treatment regimens. The Defendants nevertheless argue the POSA would read this disclosure and "immediately envisage" the particular regimen of five loading doses followed by a dose eight weeks later, as claimed in the DME Claims. The Court holds that the "immediately envisage" case law is inapplicable in this case, because the asserted reference fails to disclose all the elements of the asserted claim in *any* combination, and the large (here, infinite) number of dosing regimens disclosed in view of the absence of any preferred, narrower disclosure is such that the claimed dosing regimen would not be "immediately apparent" to the POSA. Wrigley, 683 F.3d at 1361 ("The question for purposes of anticipation is therefore whether the number of categories and components in Shahidi was so large that the combination of WS-23 and menthol would not be immediately apparent to one of ordinary skill in the art."). The '747 patent does not "expressly spell[] out a definite and limited class of compounds that enable[] a person of ordinary skill in the art to at once envisage each member of this limited

class," Eli Lilly, 471 F.3d at 1376, and therefore does not anticipate.

Additionally, as was the case with respect to the September 2009 Press Release, the POSA following the disclosure of the '747 patent would not necessarily perform the claimed regimen instead of one of the other infinite possibilities. As above, this mere possibility is insufficient to anticipate. Continental, 948 F.2d at 1269 ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); Therasense, 593 F.3d at 1332.

Furthermore, the example on which the Defendants rely—Example 17—does not disclose a method of treating DME. Supra ¶ 215. The Defendants do not identify any disclosure of "diabetic macular edema" anywhere in the '747 patent and instead seek to mix and match the disclosure of the embodiment on which they rely with generic disclosures outside that embodiment, which is improper. To anticipate, it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention—all the elements of the invention disclosed must be arranged as in the claim. Net MoneyIN, 545 F.3d at 1371.

Accordingly, the Court holds that the '747 patent does not anticipate the DME Claims.

iv. Claim 25 of the '572 Patent and Claims 11 and 19 of the '601 Patent are Invalid as Obvious

In general,

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR, 550 U.S. at 406 (quoting Graham, 383 U.S. at 17-18); see also In re Copaxone Consol. Cases, 906 F.3d 1013, 1025-29 (Fed. Cir. 2018) (a 3-times per week dosing regimen was obvious over the prior art); Hoffmann-La Roche Inc. v. Apotex Inc., 748 F.3d 1326, 1332 (Fed. Cir. 2014) (monthly dosing regiments obvious in view of the prior art); Merck & Co., Inc. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1373-75 (Fed. Cir. 2005) (extending dosing from daily to weekly obvious over the prior art).

The Court in KSR explained that while "the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls. If a court … conducts this analysis and concludes the claimed subject matter

was obvious, the claim is invalid under § 103." KSR, 550 U.S. at 407. To weigh the Graham factors to decide whether a party has met its burden of proof, the "legal determination of obviousness may include recourse to logic, judgment, and common sense," even "in lieu of expert testimony." Adapt Pharma Ops. Ltd. v. Teva Pharms. USA, Inc., 25 F.4th 1354, 1368-69 (Fed. Cir. 2022) (quoting Wyers v. Master Lock Co., 616 F.3d 1231, 1238 (Fed. Cir. 2010)). Further, while the published prior art does of course matter, "[t]he obviousness analysis cannot be confined by … overemphasis on the importance of published articles and the explicit content of issued patents." KSR, 550 U.S. at 419.

In addition, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR, 550 U.S. at 421.

The Supreme Court in KSR rejected the Federal Circuit's more rigid teaching-suggestion-motivation (TSM) test in favor of a more flexible obviousness standard, holding that "the analysis need not seek out precise teachings directed to the specific subject matter

of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR, 550 U.S. at 418. The Court also instructed that the more flexible KSR standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents," id. at 419, but that "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed," id. at 420.

Here, there is no dispute among the experts for the parties that there was market pressure to employ extended (i.e., less frequent than monthly) dosing regimens for aflibercept, given that monthly dosing with other anti-VEGF agents had already quickly fallen out of favor and extended dosing regimens were the dominant treatment paradigms with the existing therapies. (Compare Tr. 1816:4-24, 1919:7-8 (Csaky), with Tr. 773:23-774:6, 935:4-937:9 (Albini)).

In other words, the record reflects that there was motivation to employ DME-DR treatment regimens like those described in the 9-14-2009 Press Release and the '747 patent that would allow for monthly assessment and administered injections (which are without dispute uncomfortable to patients and can lead to potential irritation or infection, (Tr. 290:12-23, 292:6-19 (Csaky))), only

on those visits where the assessment indicated a need for an injection. (See DTX 2730.22; DTX 3198.2). This motivation also applies to claim 6 as well, given that DME and DR are disorders falling within the scope of claim 1. However, additional evidence of record also confirms, for AMD for example, the motivation to employ extended dosing regimens given that "[e]ach injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis. A significant time and financial burden falls on patients during their treatment course." (DTX 204.5; see also Tr. 1816:4-24 (Csaky); Tr. 773:18-774:9 (Albini); DTX 2035.1-4).

Defendants also correctly note that the DME-DR Claims do not use any terminology denoting whether or not the 5 monthly injections are "loading doses" or whether they are administered as as-needed injections. (PTX-1.21 (claims 10 and 11); PTX 1.22 (claims 18 and 19); PTX 3.25 (claims 15 and 25); Tr. 1927:23-1928:10 (Csaky)). Neither Regeneron nor its expert have identified any way to tell the difference between "fixed loading" injections and as-needed injections, in the context of every-day, routine clinical practice.[9] Indeed, the named inventor himself noted that

[9] While there may be a difference in the context of a clinical trial, where investigators are required to follow specific clinical trial protocols that distinguish between fixed, or required injections, and discretionary, as-needed injections,

PRN administration is described in the '601 and '572 patents and is one of the possible approaches both contemplated by the specification and "within the scope of the present invention." (Tr. 231:4-24 (Yancopoulos)). The Court, as a result, finds that the dosing regimens discussed by both Dr. Albini, (Tr. 782:3-784:13 (Albini) (9-14-2009 Press Release); Tr. 785:24-787:17 (Albini) ('747 patent)), and Dr. Csaky, (Tr. 1958:19-1961:24 (Csaky)), derived from both the 9-14-2009 Press Release and the '747 patent permitted doses within the range of the regimen as set forth in the DME-DR Claims.

In his anticipation analysis, Defendants' expert Dr. Albini testified that the 9-14-2009 Press Release's disclosure of 3 monthly injections, followed by PRN administration, which Regeneron's expert Dr. Csaky testified is a regimen known to involve monthly evaluation, is a regimen that a POSA could immediately envision leading to the administration of 5 monthly injections followed by one or more injections at an 8-week interval. (Tr. 780:15-784:13 (Albini); Tr. 1824:1-8 (Csaky); DTX 3198.2; DDX 6.50-55). For the same reason, Defendants correctly argued that the claimed regimen — "approximately every 4 weeks for

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Regeneron has grounded its infringement allegations in real-world clinical practice, and has not alleged that Defendants' use of the regimen in its clinical trial infringes the DME-DR Claims.

the first 5 injections followed by…approximately once every 8 weeks" — is not meaningfully or significantly different from the 3 monthly/PRN regimen disclosure of the 9-14-2009 Press Release, because when patients need 5 monthly injections in the prior art 3 monthly/PRN regimen to resolve their retinal fluid, they will receive them. (Tr. 781:19-784:13, 793:19-794:1 (Albini); DDX-6.52-55, 75).

With regard to Claim 6 the parties do not dispute that Dixon discloses the regimen. The Court also agrees with Defendants that the claimed isotonic solutions were obvious in view of the disclosures of Dixon and Hecht, as explained by Dr. Albini and Dr. Rabinow.

The record further shows that a POSA would have had a reasonable expectation of success at using the claimed regimens. First, the record shows that there already were regimens in the prior art that permitted 5 monthly injections followed by less frequent administration. (See, e.g., DTX 2035.2-3; DTX 2730.22; DTX 3198.2). With regard to claim 6, the record reflects that the VIEW Phase 3 regimen, which Regeneron does not dispute falls within the scope of claim 1, was disclosed in the prior art Dixon reference, among other references, and that the Phase 2 results, using an even less aggressive dosing strategy than the Phase 3

regimen, resulted in significant improvement in visual acuity. (See DTX 204.4).

Second, "[a] finding of a reasonable expectation of success does not require absolute predictability of success" at making the invention. Almirall, LLC v. Amneal Pharms. LLC, 28 F.4th 265, 275 (Fed. Cir. 2022); see also OSI Pharms., LLC v. Apotex Inc., 939 F.3d 1375, 1385 (Fed. Cir. 2019) (declining to hold that "data is always required for a reasonable expectation of success" or to require "absolute predictability of success"). Dr. Csaky admitted that the claimed regimens showed some efficacy. (Tr. 1822:23-1823:17 (Csaky)); see Hoffmann-La Roche Inc. v. Apotex Inc., 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness."). Dr. Csaky also admitted that aflibercept exhibited visual acuity gains in AMD using an even less aggressive dosing schedule than the Phase 3 schedule. (Tr. 1881:14-1882:20 (Csaky) (CLEAR-IT 2 had less loading doses and different design than VIEW trials); Tr. 1882:24-1883:7 (Csaky) (CLEAR-IT 2 clearly showed "activity" in terms of "effect on visual acuity"); Tr. 1974:25-1977:2 (Csaky) (positive results from CLEAR-IT 2); DTX 204.4-5). Under this standard, the Court finds that Defendants have shown a POSA would have had a reasonable expectation of success at using the claimed treatment regimens. Defendants' expert Dr. Albini testified as to several references

that reported visual acuity gains (though no such gains are required of the claims), including aflibercept references showing efficacy in DME patients with just a single intravitreal injection or in the related AMD indication with repeated intravitreal injections. (Tr. 790:25-792:2 (Albini); DTX 3102.3 ("The median improvement in BCVA was nine letters at 1 month and three letters at 6 weeks…"); see also DTX 204.3-4). The record also reflects positive results obtained with the VEGF inhibitor ranibizumab in the treatment of both AMD and DME. (See, e.g., DTX 2733.1 (mean gain of eight (8) letters in DME); DTX 3089.1, 4 (8 of 10 eyes showed visual acuity gains in DME); see also, e.g., DTX 2034.1 (mean gain of 7.2 letters in AMD); DTX 3115.1 (mean visual acuity improvement of 9.3 letters in AMD); DTX 4061.4 (various studies in AMD)).

In addition, the evidence shows that patients in the Do 2009 study achieved gains of nine letters at one month after the single injection of VEGF Trap-Eye, and that 2 of the patients achieved gains of 10 letters, while other patients achieved a gain of 9 letters; in all, 4 of the 5 patients showed gains in visual acuity. (DTX 3102.1, 3). Dr. Albini testified that these results would lead a POSA to have a reasonable expectation of success at using the claimed method to treat DME and DR. (Tr. 790:22-791:15, 791:20-792:2, 797:23-798:17, 800:23-801:5 (Albini)). It stands to

reason that if a single injection resulted in visual acuity gains, repeated monthly injections for 5 months, followed by one or more injections at an 8-week interval will also result in visual acuity gains in those same patients. (Tr. 791:20-792:2 (Albini)). With regard to AMD, Dr. Albini confirmed that the Phase 2 results with aflibercept resulted in significant visual acuity gains, and with extended intervals between injections. (DTX 204.4, 7 (Ref. 45); DTX 3173.6, 9, 12, 13, 16, 19; see also Tr. 840:15-844:23 (Albini)).

Third, Defendants have shown that the differences, if any, between the prior art and the claimed dosing regimen, do not rise to the level of being nonobvious. For the DME-DR Claims, the Defendants showed that prior art regimens, such as the as-needed regimen disclosed in the '747 Patent and the PRN regimen in the 9-14-2009 Press Release, were designed to treat until resolution of subretinal fluid, and that monthly visits and assessments could very well lead to easily envisioned situations in which a patient would require 5 monthly injections to resolve the patient's edema. (See Tr. 785:17-787:17 (Albini); DTX 2730.16 (7:52-67); DTX 2730.22 (20:16-67); DDX 6.59-61). After that initial period of treatment, treating a patient once every 8 weeks under the '747 patent protocol or the 9-14-2009 Press Release protocol is an obvious outcome where the interim monthly assessment show an

absence of fluid and monthly injections are no longer required. (Id.). Defendants' expert Dr. Albini further illustrated the obviousness of the regimens through Dr. Csaky's interpretation of claims 12 and 20, and what those claims reveal about the scope of independent claims 10 and 18, from which asserted claims 11 and 19 depend—that they included scenarios that are not substantively different from straight monthly dosing of aflibercept, which was not disputed to be in the prior art. (DTX 3198.2; see also Tr. 1957:6-21 (Csaky); DDX 6.65). For claim 6, Regeneron has not presented any evidence of differences between the prior art dosing regimens and the claimed regimens.

The facts here are analogous to those in In re Copaxone Consol. Cases, 906 F.3d 1013, 1025-29 (Fed. Cir. 2018), where the Court found dosing claims obvious over the prior art. The Court found that "[a]lthough the universe of potential GA doses is theoretically unlimited, the universe of dosages in the prior art that had clinical support for being effective and safe consisted of only two doses: 20mg and 40mg. Even if there were multiple injection frequencies not yet tested in the prior art — 1x, 2x, 3x a week etc. — these still represent a limited number of discrete permutations." Id.

Similarly, here, for the DME-DR Claims, there were a limited number of monthly injections available to a POSA for leading off

an anti-VEGF DME dosing regimen — in reality, 3-6. (See DTX 4129.2; Tr. 805:1-8 (Albini)). Everything else was provided in the prior art, including the disease (DME), the drug (aflibercept), the dose (2 mg), and the maintenance regimens (every-8-week, or as-needed). (DTX 3198.2).

The Court has also taken into consideration Regeneron's counter-arguments, including those presented by Regeneron's expert, Dr. Csaky. Dr. Csaky contends that concern over systemic side effects and potential over-treatment would have dissuaded a POSA from going with 5 monthly loading doses in the treatment of DME. (Tr. 1833:12-1835:3, 1837:11-19, 1850:7-1851:6, 1855:6-1856:16, 1956:20-1958:18 (Csaky)). While Regeneron does not style this argument as a "teaching away," that is essentially what they have presented. However, teaching away occurs only when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." L'Oréal USA, Inc. v. Olaplex, Inc., 844 F. App'x 308, 318 (Fed. Cir. 2021) (quoting In re Urbanski, 809 F.3d 1237, 1244 (Fed. Cir. 2016)). Absent evidence that the prior art "invariably" would have led to a different path, the prior art does not teach away. See PAR Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1199 (Fed. Cir. 2014).

On claim 6, the Court also has considered Regeneron's counter-arguments, and finds that those arguments are not persuasive. The testimony and evidence of record established that formulating ophthalmic solutions as isotonic would have been routine and commonplace. (DTX 3588.11, 13; see Tr. 1096:23-1098:8, 1099:15-22(Rabinow)). This is confirmed by the asserted '601 and '572 patents, which explain that "[a] multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences," and that the contemplated formulations involved the use of "excipients and carriers well known to pharmaceutical chemists." (PTX 1.13 (5:55-58; 5:66 – 6:7); PTX 3.16 (5:64-67; 6:8-17)).

Further, "a reference does not teach away if it merely expresses a general preference for an alternative invention but does not criticize, discredit or otherwise discourage investigation into the invention claimed." UCB, Inc. v. Actavis Lab'ys UT, Inc., 65 F.4th 679, 692 (Fed. Cir. 2023) (quoting DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1327 (Fed. Cir. 2009)) (internal quotation marks omitted); see also Galderma Lab'ys, L.P. v. Tolmar, Inc., 737 F.3d 731, 738-39 (Fed. Cir. 2013) (prior art did not teach away when it did not show "side effects would be serious enough to dissuade" particular use). In addition, none of Regeneron's witnesses were able to point to

anywhere in the specification of the asserted patents where the concerns over systemic side effects or over-treatment were explained or resolved, leaving the specification providing no more guidance than the prior art. Merck & Co., Inc. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1373-74 (Fed. Cir. 2005).

As Defendants correctly observe, Plaintiff's expert Dr. Csaky did not provide any documentary evidence showing that anyone in the community was actively discouraging the use of additional loading doses in the treatment of DME or DR. To the contrary, the evidence of record shows that by 2010 multiple parties had completed, or were conducting or planning, clinical trials that utilized dosing schemes that required or permitted five *or more* monthly injections. This was evident from the 9-14-2009 Press Release alone, which included a treatment arm directed to straight monthly dosing, which is an even more aggressive treatment regimen than 5 monthly injections followed by extended intervals. (DTX 3198.2; see also Tr. 803:1-5 (Albini)). In addition, the 9-14-2009 Press Release disclosed the use of the PRN regimen following three monthly injections, which a POSA would recognize as permitting 5 monthly injections were they so needed. (DTX 3198.2; see also Tr. 780:15-784:13 (Albini); Tr. 1958:19 – 1960:24 (Csaky); DDX 6.51-55). The same is true with respect to prior art ranibizumab clinical trials, some of which included either monthly

dosing or as-needed regimens that permitted 5 or more monthly injections. (DTX 2733.2 ("Patients received 3 monthly injections followed by as-needed monthly injections after month 2.")).

Dr. Csaky also suggested that the range of loading doses in the prior art was fixed at 3-4, so a POSA would not have considered 5. (Tr. 1847:4-1848:1 (Csaky)). As Defendants point out, this testimony directly contradicts that routine workers in the field were contemplating a range of 3-6 monthly doses in the first 6 months for the DME clinical trial. (Tr. 804:23-805:9 (Albini); DTX 4129.2 (suggesting 3-6 monthly doses after receiving feedback from the Swedish Medical Products Agency, DTX 226); DDX 6.92). It also contradicts the approach that physicians were taking in actual, every-day clinical practice, as Dr. Albini testified, which often involved treating a VEGF-related eye disorder monthly until retinal fluid is resolved, then switching to longer injection intervals. (Tr. 771:7-772:19 (Albini); DTX 2035.1 ("I treat with ranibizumab monthly until optical coherence tomography (OCT) shows the macula to be completely free of fluid. *Some patients reach that point after 2 injections; others require as many as 8 injections*."); DTX2035.3 ("I give as many consecutive monthly doses as necessary to dry the macula."); id. ("I see patients 4 weeks after the initial injection. If the macula is still wet at

that time, I give another injection and see them in 4 weeks."); DDX 6.36; see also DTX 3198.2; DTX 204.4; DDX 6.91).

Dr. Csaky's fixed-dosing versus individualized dose argument in response is without merit, as Federal Circuit precedent emphasizes that the prior art need only disclose the dosing mechanism to obviate the claims; the theory for the dosing schedule need not be the same. Nalpropion Pharms., Inc. v. Actavis Lab'ys FL, Inc., 934 F.3d,1344, 1354-55 (Fed. Cir. 2019). The patented methods in Nalpropion were directed towards weight loss using specific dosages of naltrexone and bupropion. Id. at 1347-48. The patentee argued that there was no motivation to combine the prior art asserted because the claimed drug did not possess sufficient efficacy to secure FDA approval for weight loss; instead, the prior art disclosed the use of drugs to curb weight gain and reduced cravings in depression. Id. at 1353-54. The Court found that it must "consider a range of real-world facts to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." Id. at 1354 (cleaned up). It further reasoned that "[t]he inescapable, real-world fact … is that people of skill in the art *did combine* [the drugs] for … goals closely relevant to weight loss … without understanding [the drugs'] mechanism of action." Id. Given the art disclosed that the drugs were "well-tolerated and safe" in a

related condition, the person of skill had the requisite motivation and reasonable expectation of success. Id. Here too, the Court finds that though the rationale behind using fixed-dosing and individualized dosing may differ, "[t]he inescapable, real-world fact … is that people of skill in the art" *did* rely on the regimen disclosures of the 9-14-2009 Press Release and/or the '747 patent, and did so in light of the safety disclosures in Dixon, among others, and efficacy disclosures in Do 2009 and Lalwani 2009b. Id. That the exact theory—fixed-dosing—was not disclosed does not negate that persons of skill in the art were indeed practicing the claims, and they did so knowing aflibercept would be "well-tolerated and safe," id., given its history disclosed in the art.

The Court further finds Dr. Csaky's purported safety concerns related to the additional loading doses unpersuasive. While both parties' experts agreed that there are always concerns regarding safety, each of the references Dr. Csaky refers to, including Do 2009 and Lalwani 2009b, refer to continuing clinical studies that were designed to further test administration of these agents in DME patients, without any suggestion to halt or discontinue clinical studies due to systemic side effect or over-treatment concerns, thus contradicting Dr. Csaky's testimony. (DTX 3102.6 ("The results of this study *strongly* support additional testing of VEGF Trap-Eye in patients with DMO in which *repeated* injections

are given at an interval of every 6 weeks or longer.") (emphasis added); DTX 2733.1-2 (describing the READ-2 study that followed the READ-1 results, parallel Phase 2 RISE and RIDE studies, and "several" investigator-sponsored trials such as RESOLVE and the study conducted by Philip Ferrone, MD, each of which involved repeated injections, and, in some cases, dose escalation)). The Do 2009 reference also notes that the purpose of the study was to assess the *safety*, tolerability and bioactivity of aflibercept and concludes that "[i]njections of VEGF Trap-Eye were well tolerated with no ocular toxicity," and the only serious systemic adverse event was graded as unrelated to the study drug. (DTX 3102.1, 3). The larger Phase 2 AMD study of aflibercept also was reported as supporting the conclusion that VEGF Trap-Eye seems to be generally well-tolerated with no serious drug-related adverse events. (DTX 204.4). It also is the case that Regeneron was proceeding with, and had already publicly announced by 2009, DME clinical trials using regimens that required more than 5 monthly injections (the DME Phase 2 monthly dosing arm) or where 3-6 monthly injections were both permitted and contemplated (the DME Phase 2 PRN following 3 monthly injections arm), thus contradicting the argument that a POSA would have felt constricted because of safety concerns from using five monthly injections to initiate DME treatment. (DTX-3198.2).

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MEMORANDUM OPINION AND ORDER FOLLOWING BENCH TRIAL

The Federal Circuit has held that "well-known, standard medical practices" are obvious, especially as it relates to addressing patient responses such as side effects and outcomes. Genentech, Inc. v. Sandoz Inc., 55 F.4th 1368, 1378 (Fed. Cir. 2022). In Genentech, the patented invention was directed towards the method of treatment of liver function abnormalities using a specific range of pirfenidone in milligrams at certain "periods," the amount changing depending on said period; a second family of patents claimed the same drug use, but in a lower dosage to "avoid[] adverse interactions" with related drugs. Id. at 1371-73, 1374-75. The alleged infringer claimed that prior art references "disclosed reescalation of dosage after temporary dose reduction for patients with" indicators of the claimed abnormalities and the "discontinu[ation of] pirfenidone only for patients" with the claimed abnormality indicators. Id. at 1376. The Federal Circuit, agreeing that the methods were disclosed in the prior art, noted "varying doses in response to the occurrence of [patient response] would seem to be a well-established, hence obvious, practice. Thus, claiming it as an invention would appear to be at best a long shot." Id. at 1376-77; see also Amgen Inc. v. Sandoz Inc., 66 F.4th 952, 968 (Fed. Cir. 2023). Here too, switching to 5 monthly loading doses followed by every-8-week dosing in DME/DR patients "in response to the occurrence" of less-

than-favorable visual acuity results with fewer initial injections would've also been obvious. Genentech, 55 F.4th at 1377. Because the asserted claims "recite adjusting doses in the presence of [unfavorable patient responses]," they too "would have been obvious in view of the prior art" which disclosed what "clinicians routinely do." Id. at 1378.

In conclusion, the Court finds that Defendants have shown, by clear and convincing evidence, that claims 11 and 19 of the '601 patent, and claim 25 of the '572 patent, are invalid as obvious in view of both the '747 Patent alone, and the 9-14-2009 Press Release alone.

The Court also finds that the Defendants have shown, by clear and convincing evidence, that claims 11 and 19 of the '601 patent, and claim 25 of the '572 patent, are invalid as obvious in view of both the '747 patent, and the 9-14-2009 Press Release, either one in combination with Do 2009 and Lalwani 2009b. For these reasons, the Court does not address whether claims 11 and 19 of the '601 patent and claim 25 of the '572 patent are invalid under § 112.

The Court also finds that the Defendants have shown, by clear and convincing evidence, that claim 6 of the 572 Patent is invalid over Dixon in view of Hecht.

Furthermore, the claimed combinations were obvious to try. In In re Copaxone, the Federal Circuit, applying the Supreme

Court's obvious-to-try standard described in KSR, affirmed the judgment of the district court in favor of the patent challengers. See generally In re Copaxone Consol. Cases, 906 F.3d 1013 (Fed. Cir. 2018). In KSR, the Supreme Court explained that:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421. The Federal Circuit explained that where "the prior art focused on two critical variables, dose size and injection frequency, and provided clear direction as to choices likely to be successful" the claimed invention is obvious to try. In re Copaxone, 906 F.3d at 1025 (Fed. Cir. 2018). The Court further explained that as of the priority date, two dose sizes had been established and the prior art was encouraging POSAs to pursue less frequent dosing. Id. Here, there is even more direction in the prior art than that in Copaxone. The prior art, including the 9-14-2009 Press Release, had identified the drug, the dose, and the indication—aflibercept, 2 mg, DME/DR. (DTX 3198.2). The prior also had identified monthly dosing. (Id.). The prior art also identified a very limited number of fixed extended dosing regimens

that had maintenance dosing phases that were keyed to multiple-month intervals: every-2-months (i.e., every-8-weeks) and every-3-months (i.e., every-12-weeks); Regeneron's expert Dr. Csaky testified that ophthalmologists were moving away from monthly administration, and testified that every-12-week administration (i.e., the PIER regimen) was viewed as inferior, leaving only every-8-week as a target fixed extended maintenance regimen. (See, e.g., Tr. 1816:4-24, 1817:22-1819:20 (Csaky) (pivot to personalized regimens to get monthly dosing visual acuity gains without office visit burden); Tr. 1870:23-1872:9, 1872:19-1873:16, 1873:22-1874:8 (Csaky) (every-3-month dosing fell out of favor)). The prior art also identified monthly loading dosing, and the key metric or rationale for determining the number of loading doses: administering until the retina appears free of fluid by OCT examination. (See, e.g., PTX 722.1-3; DTX 204.4; DTX 2730.22, 20:16-67; DTX 3115.1; DTX 3198.2; DTX 4013.1-3; DTX 4061.4; Tr. 765:13-770:19 (Albini) (describing the evolution of the art, with loading doses and early monthly dosing becoming prevalent alongside the advent of OCT)); Tr. 771:7-772:10, 773:16-774:9 (Albini) (the same in clinical practice); Tr. 804:9-22 (Albini) (highlighting a range of monthly loading doses in the art); Tr. 1844:4-9 (Csaky) (validating Dr. Albini's loading dose summary)). Moreover, the prior art had settled on a very narrow range of

possible monthly loading doses: 3-6. (See DTX 3198.1-2; DTX 4129.2).

Not only that, but the prior art, as Defendants' expert Dr. Albini testified, had been employing extended dosing regimens, in both fixed and as-needed personalized contexts (which often results in even fewer injections being administered than in a fixed regimen) and been consistently obtaining results with visual acuity improvements. (See, e.g., PTX 722.1-3; DTX 204.4; DTX 2730.22, 20:16-67; DTX 3115.1; DTX 3198.2; DTX 4013.1-3; DTX 4061.4; Tr. 765:13-770:19, 771:7-772:10, 773:16-774:9 (Albini)). Indeed, visual acuity improvements were observed with just a single injection of aflibercept in DME patients, leading to a reasonable expectation that similar outcomes would result with repeated injections. (DTX 3102.1; Tr. 798:2-17 (Albini)).

Within such a context, "a POSITA had only a limited number of permutations of dose and frequency to explore that were not already disclosed in the prior art," rendering the claimed combination obvious-to-try. In re Copaxone Consol. Cases, 906 F.3d 1013, 1025 (Fed. Cir. 2018). As the Court in Copaxone explained, the fact that a POSA could calculate unlimited numbers of permutations, in theory, was irrelevant, and it was the universe outlined by the prior art that controlled. Id. at 1026. There, the universe of dosage amounts was two. Id. Here, we have a similar number, with

the prior art 9-14-2009 Press Release reporting 0.5 mg and 2.0 mg, with a clear focus on the 2 mg dose. (DTX 3198.2).

The Copaxone court further explained that "[e]ven if there were multiple injection frequencies not yet tested in the prior art—1x, 2x, 3x a week etc.—these still represent a limited number of discrete permutations." In re Copaxone Consol. Cases, 906 F.3d 1013, 1026 (Fed. Cir. 2018). Here, the Court notes that the fact of there being a limited number of monthly loading dose permutations available, a POSA would have found five loading doses to be obvious-to-try. This is particularly so in view of the use of 3-4 in treating AMD, and the common knowledge among POSAs, including Plaintiff's expert Dr. Csaky, that DME often required additional injections. (See, e.g., DTX 204.4; DTX 2733.3; Tr. 1853:7-15 (Csaky).

Copaxone further instructs that "conclusive proof of efficacy is not necessary to show obviousness" but that "[a]ll that is required is a reasonable expectation of success." In re Copaxone Consol. Cases, 906 F.3d 1013, 1026 (Fed. Cir. 2018) (cleaned up). The prior art presented here by Defendants' expert Dr. Albini also shows that a POSA would have had a reasonable expectation of success at using a regimen of 5 monthly injections followed by every-8-week injections in the treatment of DME. (See DTX 204.4;

DTX 2034.1; DTX 2733.1-2; DTX 3102.1; DTX 8190.3; Tr. 798:2-801:5 (Albini)).

On claim 6, the Court finds that the use of isotonic formulations also represents an obvious-to-try approach. The record evidence establishes that Dixon discloses the claimed dosing regimen, and also that the formulation used in that dosing regimen is comfortable and non-irritating to the eye. (DTX 204.3-4). When it comes to tonicity, a POSA has three options: hypotonic, isotonic, or hypertonic. (See Tr. 212:14-24 (Yancopoulos) (noting options for osmolality); see also Tr. 1168:14-1169:2 (Rabinow) (distinguishing isotonic and hypertonic, but equating isotonic and iso-osmolar)). Given Dixon's guidance that a formulation ought to be comfortable and non-irritating, and Hecht's instruction that ophthalmic formulations should be isotonic, the hypotonic (not enough solute) and hypertonic (too much solute) options fall by the wayside, with the focus of the prior art primarily on isotonic. Accordingly, with isotonicity being a routine and commonplace aspect of ophthalmic formulations, and a limited number of permutations in the prior art for tonicity, the use of isotonic formulations for aflibercept becomes obvious-to-try. In re Copaxone Consol. Cases, 906 F.3d 1013, 1025 (Fed. Cir. 2018) (cleaned up).

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In view of the evidence, the Court finds that claims 11 and 19 of the '601 patent, and claim 25 of the '572 patent, are invalid as being drawn to combinations that are obvious to try in view of the directions and guidance of the prior art, including the 9-14-2009 Press Release, which provided POSAs with the drug, the dosage amount, the disease, and the 8-week maintenance dosing regimen. If Plaintiff contends that the only missing element was an express recitation of 5 monthly loading doses, that would have been provided by the general knowledge of those of ordinary skill in the art about the small number of permutations available for monthly loading doses.

Likewise, the Court finds that, due to the limited number of permutations in the prior art for tonicity of ophthalmic formulations, and the clear direction provided by the prior art, including Dixon and Hecht, claim 6 is invalid for being drawn to subject matter that would have been obvious to try.

Accordingly, claims 11 and 19 of the '601 patent, and claims 6 and 25 of the '572 patent, are invalid under 35 U.S.C. § 103.

The Court also weighs, as it must, any evidence or testimony of record relating to secondary considerations. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007). The Court's presentation of the parties' secondary considerations arguments follows.

Defendants assert that there was no evidence of secondary considerations presented at trial that would be sufficient to overcome the demonstrated obviousness of the asserted claims of the '601 and '572 patents.

Defendants point to the testimony of Plaintiff's expert Dr. Csaky, notably the fact that Dr. Csaky only presented purported evidence of long-felt need, failure of others, and industry praise during the Plaintiff's rebuttal case, and that the evidence was limited to aspects of the claims that were already in the prior art. (See Tr. 1914:4-1919:11 (Csaky)).

Regeneron argues that the claimed dosing regimen fulfilled a long-felt need for a reliable, fixed extended dosing regimen for the treatment of any angiogenic eye disorder. Regeneron's expert Dr. Csaky explained that no regimen prior to Regeneron's Q8 scheme equated to monthly dosing's outcomes. (Tr. 1914:12-17 (Csaky)). He elaborated that alternatives in the prior art such as treat-and-extend and PRN did not fulfill such a need, mostly because the ophthalmologist was required to "always … have [their] OCT to make … treatment decisions." (Tr. 1914:18-1915:6, 1915:21-1916:4 (Csaky)). Regeneron supplemented its long-felt need arguments by positing that its competitors had tried and failed to develop an extended dosing regimen like that claimed in the '601 and '572 patents. Regeneron points to testimony from its expert, Dr. Csaky,

who commented on his own failures with siRNA technologies as it related to inhibition of VEGF, but did not elaborate on the schedule for the same. (Tr. 1828:7-15 (Csaky)). Dr. Csaky further commented on the failure of Macugen to fulfill such a need because the data for the six-week intervals were "quite poor." (Tr. 1916:7-25 (Csaky)). He clarified that a subsequent 12-week dosing regimen lacked any data, and thus also constituted a failure. (Tr. 1917:1-5 (Csaky)).

Regeneron alternatively relied on safety concerns in support of its failure of others claims, relying again on Dr. Csaky's testimony. Dr. Csaky began by commenting that there had been multiple failures "through the history" of anti-VEGF research and use, but identified only a single instance where safety concerns were raised. (Tr. 1828:16-20 (Csaky)). Dr. Csaky exclusively relied on the case of Beovu, which he described as a "weirdo" molecule, to suggest that developers failed to augment anti-VEGF therapy. (Tr. 1828:21-1829:12 (Csaky)). Again, this testimony did not mention the dosing regimen at which Beovu was administered.

Regeneron did not present any evidence of unexpected results in its rebuttal; though its expert Dr. Csaky discussed various clinical trials and internal documents disclosing study results, he did not characterize any as specifically relevant to this

secondary consideration, nor did he explain how any of those results would not have been expected in light of the prior art.

Regeneron cited multiple publications that comment on the reaction to Eylea after it had launched. Regeneron's expert Dr. Csaky first identified comments from the Food and Drug Administration and underscored that it "recognized that [Regeneron's] two-month dosing schedule was the same as monthly dosing schedule." (Tr. 1917:12-18 (Csaky)).

Dr. Csaky likened the regulatory disclosure to other publications by his colleagues. (Tr. 1917:19-21). The sole reference he presented in response was the Ohr and Kaiser 2012 publication (PTX 841), which discussed the visual acuity gains from use of aflibercept compared to ranibizumab. (Tr. 1918:3-13). The study disclosed that aflibercept, dosed every two months, was non-inferior to monthly ranibizumab. (See PTX 841.1).

Regeneron further introduced the Thomas publication (PTX 1155) into evidence during its discussion of industry praise. Thomas discloses the cost-effect analysis in regard to ranibizumab, bevacizumab, and aflibercept—the major anti-VEGF agents used to treat angiogenic eye disorders. (PTX 1155.5). Though Thomas notes that "clear savings can be seen" with aflibercept, it subsequently highlights that bevacizumab is the most affordable treatment, and that "all three therapies are

considered to have equal efficacy across the board based on studies and clinical data that have been evaluated." (Id.)

Defendants note that Dr. Csaky's discussion of long-felt need was limited to a discussion of a purported long-felt need for a fixed extended dosing regimen. (Tr. 1914:12-1915:6, 1915:21-1916:4 (Csaky)). Defendants respond to this testimony by pointing to several shortcomings.

First, Defendants note that for this discussion, Dr. Csaky did not rely upon any documents or evidence to support his claims of there being a long-felt need, and that Dr. Csaky's expert report in this regard was limited to addressing AMD, not DME or DR. (Tr. 831:6-13, 839:24-840:7 (Albini); DDX 6.147). Accordingly, Defendants renew their motion *in limine* seeking to preclude Dr. Csaky from testifying on matters outside the scope of testimony provided in his expert reports and relying on secondary considerations testimony untethered to the novel features of the asserted claims of the dosing patents. (Dkt. 506). Therasense, Inc. v. Becton, Dickinson & Co., 593 F.3d 1325, 1336 (Fed. Cir. 2010) (evidence of long-felt need failed "because it [was] not 'commensurate in scope with the claims which the evidence is offered to support'" (quoting In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983))); Merck & Cie v. Gnosis S.P.A., 808 F.3d 829,

838 (Fed. Cir. 2015) (long-felt need must be tied to novel claim elements).

Second, Defendants highlight that the "fixed extended dosing regimen" concept, which is the sole basis for Dr. Csaky's long-felt need opinions, was already disclosed in the prior art, and thus cannot form the basis for a showing of long-felt need. BTG Int'l Ltd. v. Amneal Pharms. LLC, 923 F.3d 1063, 1076 (Fed. Cir. 2019) ("[B]ecause other treatments for [the claimed indication] were available, the evidence presented here does not establish that there was a specific unsolved, long-felt need for the treatment."). For example, Defendants' evidence of record, including the prior art 2009 Dixon reference, disclosed to the public the use of fixed every-8-week dosing following a series of 3 monthly injections in the treatment of AMD. (DTX 204.4 ("2.0 mg at an 8 week dosing interval (following three monthly doses)"); see also Tr. 812:12-813:3 (Albini); DDX 6.116-119). Additional evidence of record presented by Defendants and their expert Dr. Albini includes the 9-14-2009 Press Release, which disclosed the same type of fixed regimen (i.e., 8-week injection intervals) in the treatment of DME. (DTX 3198.2 ("2 mg every eight weeks after three monthly loading doses"); see also Tr. 780:24-781:13; DDX-6.51). According to Defendants, such evidence, because it was in the prior art, as a matter of law cannot form the basis for any

secondary indicia of non-obviousness. See, e.g., Merck & Cie v. Gnosis S.P.A., 808 F.3d 829, 838 (Fed. Cir. 2015) (long-felt need must be tied to novel claim elements).

Third, Defendants point to Dr. Csaky's failure to show nexus, or in other words, to tie any of the purported long-felt need to the aspects of the asserted claims that are purported by Plaintiffs to be novel and absent from the prior art: isotonicity of the formulation (claim 6 of the '572 patent) and five "loading doses" spaced a month apart in the treatment of DME or DR (claim 25 of the '572 patent; claims 11 and 19 of the '601 patent). (See Dkt. 506).

Fourth, Defendants observe that Dr. Csaky did not dispute the evidence presented by Defendants' expert Dr. Albini showing there to be extended dosing regimens and approaches in use in the prior art that were capable of achieving visual acuity gains while minimizing injections or office visits, or in the case of "treat-and-extend," both. (Tr. 831:6-837:8 (Albini); PTX 722.2-3 ("Dr. Brown: … I treat and extend from the start. I give 3 monthly injections and see them in 8 weeks."); DTX 2040.24; DTX 3131.1, 4, 14; DTX 4113.8; DTX 4192.18; DTX 4194.13; DDX 6.136-147). Instead, Dr. Csaky attempted to narrow the scope of the asserted DME-DR Claims to regimens that were "fixed," where the 5 monthly injections are "loading doses," or where the claims exclude monthly

office visits. (Tr. 1816:4-24 (Csaky) (general goals and office visits); Tr. at 1861:7-1863:11 (Csaky) (limits in regard to the '747 patent); Tr. 1863:12-1865:15 (Csaky) (limits in regard to the 9-14-2009 Press Release); Tr. 1914:12-17 (Csaky) (focusing secondary considerations analysis on "fixed extended dosing regimen[s]")).

Defendants note that Plaintiff never sought during the claim construction phase of litigation to construe the claims to import the limitation "fixed," or to exclude uses in which monthly office visits occur, (Dkt. 124; Dkt. 174-2), and did not proffer such constructions at trial. As a result, Defendants urge that any effort by Plaintiffs to distinguish the prior art based on any such imported language should be rejected. See Key Pharms. v. Hercon Lab'ys Corp., 161 F.3d 709, 715 (Fed. Cir. 1998) (explaining "the doctrines of law … bar parties from fundamental changes in positions asserted at trial" and during claim construction, such as offering a new, alternative construction in post-trial briefing to "salvage" a party's case). Defendants further note that Plaintiff's approach is inconsistent with Plaintiff's presentation of its infringement case, where it did not see the need to distinguish allegedly infringing uses in which aflibercept was administered every 8 weeks in a "fixed" regimen from apparently non-infringing uses in which aflibercept was administered in a

personalized regimen where the intervals happened to fall every 8 weeks; Plaintiff also failed to see the need to find the concept of skipped office visits or the terms "loading doses" and "fixed" administration in Defendants' proposed prescribing information. (Dkt. 581, 20-28).

Fifth, Defendants point to Dr. Csaky's concession that "treat and extend and prn were clearly the dominating treatment regimens," and to the extent the 8-week fixed dosing regimen is ever used, it is only infrequently, in "certain settings with certain patients." (Tr. 1918:19-1919:11 (Csaky)). Defendants also note that Dr. Csaky could only tie that infrequent use to the rare situations where, for example, an OCT machine is not working. (Tr. 1914:18-1915:6, 1915:21-1916:4 (Csaky)). According to Defendants, the at worst non-existent, and at best very infrequent, use of the claimed 8-week regimen, cannot be grounds for a showing of long-felt need. (See Tr. 836:20-837:8 (Albini) (long-felt need met); DDX 6.147).

Lastly, Defendants argue that Regeneron's evidence is not commensurate in scope with claim 1 (from which claim 6 depends). Claim 1 is drawn to all angiogenic eye disorders, including some for which no successful clinical trials have been run, and some for which aflibercept has not demonstrated efficacy. (Tr. 1273:13-1275:22, 1276:7-1277:7, 1279:2-1280:15 (Stewart); Tr. 1887:25-1888:5, 1985:18-1993:2 (Csaky); see also, generally DTX 5429; DTX

5430; DTX 5431; DTX 9033; DTX 9034; DTX 9035). According to Defendants, reliance on a purported long-felt need for an extended dosing regimen for one or two disorders is not a sufficient representation of the claimed genus, and the evidence thus is not commensurate in scope with the claimed subject matter. Asyst Techs., Inc. v. Emtrak, Inc., 544 F.3d 1310, 1316 (Fed. Cir. 2008) (citing In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983)).

Defendants thus argue that Plaintiffs have not met their burden of showing that any long-felt need existed for the claimed dosing regimens as of January 2011, and certainly have not presented long-felt need evidence sufficient to overcome the showing of obviousness made by Defendants.

On failure of others, Defendants respond to the testimony of Plaintiff's expert by pointing to many of the same shortcomings that plagued Plaintiff's long-felt need evidence, including, *inter alia*: there was no evidence presented of any failure to develop an isotonic formulation or failure to administer 2 mg of aflibercept every 4 weeks for the first 5 injections in the treatment of DME; the "fixed extended" dosing concept involving 8-week injection intervals already had been published; and Dr. Albini's unrebutted testimony that regimens existed in the prior art, including PRN, which eliminated the need for monthly injections, and treat-and-extend, which eliminated the need for both monthly injections and

monthly office visits. (See DTX 204.4; PTX 722.2-3 ("Dr. Brown: … I treat and extend from the start. I give 3 monthly injections and see them in 8 weeks."); DTX 2040.24; DTX 3131.1, 4, 14; DTX 3198.2; DTX 4113.8; DTX 4192.18; DTX 4194.13; see also Tr. 831:6-838:21 (Albini)).

Defendants also point to the testimony of Plaintiff's expert Dr. Csaky, which Defendants argue is lacking, because Dr. Csaky's opinions include only a high-level discussion of Macugen, a drug that had fallen out of favor years prior to the approval of aflibercept. (Tr. 1916:17-1917:5 (Csaky)). However, Dr. Yancopoulos admitted that Macugen was a "game changer." (Tr. 122:8-14 (Yancopoulos)). Even if Macugen was a failure, this was resolved by the success of ranibizumab. (Tr. 122:8-14 (Yancopoulos) ("Macugen sort of disappeared because the Lucentis was better."). And physicians had being using ranibizumab to treat angiogenic eye disorders, after any so-called failure of Macugen. (See PTX 722).

Dr. Csaky also pointed to the failure of Beovu, a drug that experienced post-approval safety issues. (Tr. 1828:21-1829:12 (Csaky)). Dr. Csaky admitted that Beovu (brolucizumab) was a "weirdo kind of molecule," but did not attribute the failure to the dosing regimen. (Tr. Id.) Defendants also point to the testimony of their own expert, Dr. Albini, which they note has

gone unrebutted, about the availability of extended dosing regimens, including treat and extend, that allow for personalized treatment while minimizing the need for both injections and office visits. (Tr. 831:6-837:8 (Albini); PTX 722.2-3 ("Dr. Brown: … I treat and extend from the start. I give 3 monthly injections and see them in 8 weeks."); DTX 2040.24; DTX 4113.8 ("In the 'treat-and-extend' approach … treatment is administered at each patient visit, even in the absence of macular edema. If the macula remains free of edema, and the vision is stable, the interval between visits is extended to a maximum of 10-11 weeks."); DTX 4194.13; DTX 3131.14 ("There are other strategies that may yield similar or even better VA outcomes and that require fewer visits. One such strategy is known as *treat and extend*, which is particularly appealing for use in routine clinical practice."); DTX 3215.2 (treat and extend results in "fewer patient visits and treatments than monthly dosing")).

On unexpected results, Defendants note that Dr. Csaky failed to present any such unexpected results testimony during Plaintiff's rebuttal case, and failed to present any testimony as to what constitutes the closest prior art or how any results compare to the closest prior art. (Tr. 1921:17-1922:5 (Csaky)).

In addition, Defendants point to the evidence presented by Defendants' expert Dr. Albini, and his testimony regarding the

lack of unexpected results. For example, Dr. Albini testified as to the prior art disclosures of the positive results obtained with aflibercept in treating AMD patients in a Phase 2 clinical trial, using a regimen that involved even less frequent dosing than the regimen used in the Phase 3 clinical trial. (Tr. 842:3-10 (Albini); DTX 204.4 (reporting the results of the Phase 2 CLEAR-IT-2 clinical trial); see also, generally DTX 2733; DTX 3102; DTX 3115; DTX 4061; DDX 6.150-152). Specifically, Dr. Albini pointed to the 2009 Dixon prior art reference for its disclosure that patients who were treated with just 4 monthly doses, followed by PRN dosing, where patients received, on average, just 1.6 injections over the remainder of the one-year trial, achieved average visual acuity gains of 9.0 ETDRS letters, and 29% gained ≥ 15 letters by 52 weeks. (Tr. 840:18-841:21, 940:13-941:3 (Albini); DTX 204.4; DDX 6.151). Dr. Albini also testified regarding disclosures in Dixon that the median time to first re-injection in all Phase 2 patient groups was 110 days, or about 15-16 weeks, an interval longer than the claimed 8-week intervals, undermining any claims of unexpected results for the 8-week dosing regimens. (Tr. 841:22-25, 941:4-11 (Albini); DTX 204.4; DDX 6.153). Dr. Albini's testimony on the positive data resulting from the aflibercept Phase 2 clinical trial went unrebutted.

During cross examination, Plaintiff's expert Dr. Csaky conceded that the Phase 2 clinical trial results demonstrated that some patients required no injections at all during the PRN phase of the trial (i.e., between week 12 and week 52), meaning some patients went 40 weeks without requiring an injection of aflibercept. (Tr. 1977:7-1978:5 (Csaky); DTX 3173.12). Dr. Csaky also conceded that the median time to reinjection just in the Q4 loading arm was 150 days, or about 5 months. (Tr. 1978:6-13 (Csaky); DTX 3173.13). Dr. Csaky further conceded that 100% of the patients in the Q4 loading arm of the CLEAR-IT-2 trial achieved the commonly used clinical trial endpoint of fewer than 15 letters lost. (Tr. 1978:14-21 (Csaky); DTX 3173.19).

Defendants underscore that even if Plaintiff attempts to rely upon any purported unexpected results based on the Phase 3 AMD clinical trial results, those results were published in the prior art, along with a disclosure that VEGF Trap-Eye was an iso-osmotic formulation, and was the formulation used in the Phase 3 clinical trials. (Tr. 1979:12-1981:1 (Csaky); DTX 917.1-2; DTX 918.1). According to Defendants, Plaintiff has not adduced at trial evidence or testimony that establishes a conception and reduction to practice date prior to November 22, 2010 (the publication date of the disclosures in DTX 917) for claim 6 of the '572 patent. Defendants further note that Plaintiff has argued that dosing

regimens in the prior art are not anticipating without knowing the results of Phase 3 clinical trials. (Tr. 1885:3-1887:7 (Csaky) (arguing lack of anticipation because Dixon was "unclear" as to the "ability" of alternative dosing strategies, and "th[e] question about efficacy was definitely on our minds" after the VIEW trial disclosures)). To the extent that the Court credits that argument, then Defendants argue that no such Phase 3 results are found in the '601 or '572 patents for either DME or DR, and Plaintiff has therefore failed to establish a conception and reduction to practice date prior to the publication date of any such Phase 3 DME or DR results.

Although Plaintiff's expert Dr. Trout was not qualified as an expert with regard to the dosing patents, Dr. Trout offered testimony that the low levels of observed side effects for Eylea during the VIEW Phase 3 clinical trials were unexpected based on prior art knowledge of fusion proteins. (Tr. 2086:13-25 (Trout)). First, this testimony, to the extent it was intended as secondary indicia evidence, was never tied to the asserted DME-DR Claims. (See Dkt. 506). Second, this testimony was not specific as to timeframe, and the evidence of record, including other testimony adduced at trial, shows that the side effect profile of aflibercept had already been tested, described and disclosed prior to 2011. For example, on cross examination, Plaintiff's other expert Dr.

Csaky admitted that the prior art Phase 2 aflibercept trial had shown there to be no serious systemic adverse events that were deemed drug-related. (Tr. 1978:22-1979:1 (Csaky); DTX 3173.26). DTX 3173 also reported that aflibercept was "[g]enerally well tolerated with no drug-related serious adverse events." (DTX 3173.28). Likewise, the 2009 Dixon reference disclosed that aflibercept used in Phase 1 AMD trials showed that "[n]o adverse systemic or ocular events were noted" and "[n]o serious adverse events or ocular inflammation was identified during the study." (DTX 204.3). Similarly, for Phase 2, Dixon reported that "[b]ased on Phase II study data, VEGF Trap-Eye seems to be generally well tolerated with no serious drug-related adverse events," (DTX 204.4), similar to reporting from Regeneron itself, which disclosed in April 2008 that "VEGF Trap-Eye was generally safe and well tolerated and there were no drug-related serious adverse events." (DTX 2731.1).

Moreover, Regeneron has not managed to beat the bar set by monthly dosing; the claimed regimens are the same as all the other regimens previously disclosed in terms of efficacy. (See DTX 915.7 ("The VEGF-Trap outcomes are essentially the same as ranibizumab. Furthermore, the results are very similar to the many clinical trials that have already assessed ranibizumab and other anti[-]VEGF agents ... The study is a non-inferiority trial, not a

superiority trial. Statistically significant superiority to ranibizumab was not shown."); DTX 915.11 ("[Y]ou say that aflibercept will decrease treatment burden. So does PRN dosing which is the primary way Lucentis and Avastin are used.")..

Lastly, Defendants argue that Regeneron's evidence is not commensurate in scope with claim 1 (from which claim 6 depends), which is drawn to all angiogenic eye disorders, including some for which no successful clinical trials have been run, and some for which aflibercept has not demonstrated efficacy. (Tr. 1273:13-1275:22, 1276:7-1277:7, 1279:2-1280:15 (Stewart); Tr. 1887:25-1888:5, 1985:18-1993:2 (Csaky); see also, generally DTX 5429; DTX 5430; DTX 5431; DTX 9033; DTX 9034; DTX 9035). According to Defendants, reliance on any unexpected results for AMD or DME is not a sufficient representation of the claimed genus, and the evidence thus is not commensurate in scope with the claimed subject matter. Asyst Techs., Inc. v. Emtrak, Inc., 544 F.3d 1310, 1316 (Fed. Cir. 2008) (citing In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983)).

Defendants also point to the absence of any testimony or evidence from Plaintiff's experts of industry praise for the isotonicity of the Eylea formulation or for the use of five initial doses spaced a month apart in the treatment of DME or DR.

Specifically, Defendants point to where Dr. Csaky directed his testimony to purported praise from the FDA and from an Ohr & Kaiser publication about the 8-week dosing interval. (Tr. 1917:12-1918:13 (Csaky)). Defendants again highlight the fact that the 8-week dosing interval that Plaintiff points to in those references was disclosed in the prior art, and therefore was not a novel or inventive feature of the claims. (See, e.g., DTX 204.4; DTX 2730.22, 20:16-67; DTX 3198.2; Tr. 761:22-763:12, 770:4-19, 777:5-12, 780:15-782:10, 784:14-786:22, 812:12-813:3 (Albini)). In addition, Defendants argue that to the extent the praise was directed to the VIEW clinical trial results, those results were published in the prior art, and Plaintiff has not adduced at trial evidence or testimony that establishes a conception and reduction to practice date for claim 6 of the '572 patent that is prior to the November 22, 2010 publication date of the evidence in DTX 917. (Tr. 1979:12-1981:1 (Csaky); DTX 917.1-2; DTX 918.1). In addition, as Defendants' expert Dr. Albini testified, the praise that Dr. Csaky discusses was directed to different subject matter than what is set forth in the claims, and aspects or properties of the aflibercept molecule, which is the subject of much earlier patents, all of which have now expired. (Tr. 845:1-18, 848:25-850:12, 850:21-852:14 (Albini); DTX 2062.105; DTX 2730.32; DTX 4116.32; DTX 4900.57). Dr. Albini further testified that Dr. Csaky's

testimony and documents that Dr. Csaky relied upon were silent as to industry praise for EYLEA's isotonicity or for the use of 5 monthly injections in the treatment of DME or DR. (Tr. 846:12-19 (Albini)).

Defendants argue that in view of these deficiencies and the inability of Plaintiff's expert Dr. Csaky to tie any of the objective indicia to the purportedly novel aspects of the asserted claims, Plaintiff has not met its burden of showing secondary considerations sufficient to overcome the showing of obviousness presented by Defendants with respect to the asserted claims of the '601 and '572 patents.

The Court also weighs, as it must in its obviousness analysis, any evidence or testimony of record relating to secondary considerations. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007). However, "secondary considerations of nonobviousness … simply cannot overcome a strong prima facie case of obviousness." Wyers v. Master Lock Co., 616 F.3d 1231, 1246 (Fed. Cir. 2010). Further, to weigh against a finding of obviousness, "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." In re Patel, 566 Fed. App'x 1005, 1011 (Fed. Cir. 2014); see also In re Dill, 604 F.2d 1356, 1361 (C.C.P.A. 1979) ("The evidence presented to rebut

a prima facie case of obviousness must be commensurate in scope with the claims to which it pertains.").

"But there is a more fundamental requirement that must be met before secondary considerations can carry the day. For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the *claimed invention.* Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." In re Huai-Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quotations and internal citations omitted) (emphasis added); see also Novartis AG v. Torrent Pharms. Ltd., 853 F.3d 1316, 1330-31 (Fed. Cir. 2017) ("In evaluating whether the requisite nexus exists, the identified objective indicia must be directed to what was not known in the prior art"); In re GPAC, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("[F]or objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention."). Even "impressive" evidence of secondary considerations is not "entitled to weight" unless "it is relevant to the claims at issue." In re Paulsen, 30 F.3d 1475, 1482 (Fed. Cir. 1994).

Secondary considerations "when considered with the balance of the obviousness evidence in the record, guard as a check against hindsight bias." In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1079 (Fed. Cir. 2012). However, the mere fact that a party has presented some evidence of secondary considerations does not mean that such evidence controls; all of it must be weighed. See, e.g., id. (court must consider "all relevant evidence, including that relating to the objective considerations"); Genentech, Inc. v. Sandoz Inc., 55 F.4th 1368, 1378 (Fed. Cir. 2022) ("[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness.") (internal citations and quotation marks omitted); Sealy Tech., LLC v. SSB Mfg. Co., 825 Fed. App'x 795, 800 (Fed. Cir. 2020) (same); NantKwest, Inc. v. Lee, 686 Fed. App'x 864, 873 (Fed. Cir. 2017) ("Moreover, secondary considerations ... cannot overcome a strong prima facie case of obviousness.") (internal citations and quotation marks omitted); Ohio Willow Wood Co. v. Alps S., LLC, 735 F.3d 1333, 1344 (Fed. Cir. 2013) ("[W]here a claimed invention represents no more than the predictable use of prior art elements according to established functions, … evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness."); Stone Strong, LLC v. Del Zotto Prods. of Fla., Inc., 455 Fed. App'x 964, 971 (Fed. Cir.

2011) (noting "secondary considerations are inadequate to establish nonobviousness as a matter of law" where a strong prima facie case of obviousness is shown); Stamps.com Inc. v. Endicia, Inc., 437 Fed. App'x 897, 905 (Fed. Cir. 2011) (evidence of secondary considerations is "inadequate to overcome" a "strong showing of obviousness"); Agrizap, Inc. v. Woodstream Corp., 520 F.3d 1337, 1344 (Fed. Cir. 2008) ("[O]bjective evidence of nonobviousness simply cannot overcome … a strong prima facie case of obviousness"); Leapfrog Enters., Inc. v. Fisher-Price, Inc., 485 F.3d 1157, 1162 (Fed. Cir. 2007) ("[G]iven the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion that [the claim] would have been obvious."); DyStar Textilfarben GmbH & Co. Deutscheland KG v. C.H. Patrick Co., 464 F.3d 1356, 1371 (Fed. Cir. 2006) ("[S]econdary considerations of nonobviousness are insufficient as a matter of law to overcome our conclusion that the … claim [at issue] would have been obvious."); Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1484 (Fed. Cir. 1997) ("The unexpected results and commercial success of the claimed invention, although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious.")

Here, the Court agrees with the Defendants that Plaintiff has not tied any of the asserted secondary indicia to the aspects of the claims that Plaintiff has relied upon to attempt to distinguish the asserted claims from the prior art: the isotonicity of the formulation (claim 6 of the '572 patent), and 5 monthly "loading doses" (claims 11 and 19 of the '601 patent, and claim 25 of the '572 patent. As a result, Plaintiff has not established the required nexus that must be shown between the secondary indicia and any novel aspects of the claims. In re Huai-Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011); Vanda Pharms. Inc. v. Teva Pharms. USA, Inc., No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023) (industry praise must be tied to claimed method).

In addition to the lack of a demonstrated nexus, the Court agrees with Defendants that the secondary considerations evidence presented by Plaintiff is not commensurate in scope with the claims, including claim 6, which is drawn to all angiogenic eye disorders. Defendants correctly point out that the long list of angiogenic eye disorders, (e.g., PTX3.16, 5:30-48), include some for which no clinical trials have never been run, and some for which aflibercept has not demonstrated efficacy. (Tr. 1273:13-1275:22, 1276:7-1277:7, 1279:2-1280:15 (Stewart); Tr. 1887:25-1888:5, 1985:18-1993:2 (Csaky); see also, generally DTX 5429; DTX

5430; DTX 5431; DTX 9033; DTX 9034; DTX 9035). This renders Plaintiff's focus on a narrow set of disorders for its secondary considerations case insufficient to represent the full scope of the claimed genus, and the evidence thus is not commensurate in scope with the claimed subject matter. Asyst Techs., Inc. v. Emtrak, Inc., 544 F.3d 1310, 1316 (Fed. Cir. 2008) (In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983)).

Evidence that the industry praised a claimed invention is relevant to the obviousness analysis because industry participants are unlikely to praise an obvious development over the prior art. Apple Inc. v. Samsung Elecs. Co., Ltd., 839 F.3d 1034, 1053 (Fed. Cir. 2016). However, for the praise to be relevant it must be tied to the claimed invention, here the claimed methods. Vanda Pharms. Inc. v. Teva Pharms. USA, Inc., No. 2023-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023) (industry praise must be tied to claimed method).

For example, the industry praise that Plaintiff and its expert Dr. Csaky point to say nothing of isotonicity or DME-DR loading doses, and appear to instead be directed to either properties of the aflibercept molecule itself, which the Court understands was the subject of earlier-filed and now-expired patents, or the VIEW two-month dosing interval and results of that trial. (Tr. 845:1-18, 846:12-19, 848:25-850:12, 850:21-852:14 (Albini); DTX 204.5;

DTX 2062.105; DTX 2730.32; DTX 2731.1; DTX 4116.32; DTX 4900.57). The two-month dosing interval was in the prior art, a fact not disputed by Plaintiff, and the asserted claims are not drawn to any particular visual acuity levels. In any event, the VIEW clinical trial results were in AMD, and therefore not relevant to the subject matter of the DME-DR Claims.

Failure of others to solve "the problem that a patent purports to solve," is relevant to the obviousness analysis. In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1082 (Fed. Cir. 2012). "The purpose of evidence of failure of others is to show 'indirectly the presence of a significant defect in the prior art, while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan.'" Id. (quoting Symbol Techs., Inc. v. Opticon, Inc., 935 F.2d 1569, 1578-79 (Fed. Cir. 1991)). The failure of others analysis requires that the Court define the problem the patent purports to solved. Mintz v. Dietz & Watson, Inc., 679 F.3d 1372, 1378 (Fed. Cir. 2012). "Long-felt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." In re Cyclobenzaprine

Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1082 (Fed. Cir. 2012).

However, when the need was already satisfied by the prior art or the differences between the prior art and the claimed invention are minimal, there cannot be any long-felt unmet need. Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC, 618 F.3d 1294, 1304 (Fed. Cir. 2010) ("Where the differences between the prior art and the claimed invention are as minimal as they are here, however, it cannot be said that any long-felt need was unsolved."); Cubist Pharms., Inc. v. Hospira, Inc., 805 F.3d 1112, 1126 (Fed. Cir. 2015) ("[D]aptomycin treatment regimens that were only slightly different from Cubist's had previously been shown to be effective against a variety of bacterial infections. Although the prior art daptomycin treatment methods had not proved effective for SAE, the court noted that SAE is the target infection in only about 5% of the cases in which daptomycin is administered. Accordingly, the court concluded that any "long-felt need" or "unexpected results" applied only to the small percentage of cases in which daptomycin was used to treat SAE.")

Likewise, with failure of others and long-felt need, no evidence was presented that others failed or had a long-felt need for an isotonic formulation of aflibercept or for a regimen that included 5 initial monthly doses for the treatment of DME or DR.

In addition, the Court agrees with Defendants that the purported failures that Dr. Csaky points to, such as Macugen and Beovu, lack relevance. First, the testimony presented at trial shows that Macugen was an early generation anti-VEGF therapy, and a poor VEGF blocker, based on different technology than aflibercept and ranibizumab; that technology had largely fallen out of favor, being supplanted by ranibizumab and off-label bevacizumab years before aflibercept was approved. (See Tr. 122:5-14 (Yancopoulos); Tr. 763:16-764:17 (Albini)). The Court does not find the limited Macugen evidence persuasive, including because of the timing of the purported Macugen failure. Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc., 903 F.3d 1310, 1341 (Fed. Cir. 2018) (evidence "'not particularly probative' because the [failed] study preceded publications that would render the invention obvious to those of skill in the art"). Second, expert testimony established that the use of Beovu, also a different technology than ranibizumab or aflibercept, was discontinued because of safety risks, and not because of a failure to develop a DME regimen of 5 monthly injections followed by every-8-week dosing, a failure to make an isotonic formulation, or a failure to come up with an extended dosing regimen. (Tr. 861:10-21 (Albini); Tr. 1828:21-1829:12 (Csaky)).

Moreover, Plaintiff's expert Dr. Csaky did not address Dr. Albini's numerous examples of extended dosing regimens in the art that met any purported need for an extended dosing regimen, other than to testify that these examples were not examples of "fixed" dosing. The absence of the language "fixed" in the asserted DME-DR Claims has been noted elsewhere in this opinion, and the Court declines to read such language into the claims. The Court also is persuaded that the prior art regimens that Dr. Albini presented, including the widespread use of PRN and treat-and-extend, show that the need had been met for extended regimens that reduce the need for monthly injections (in the case of PRN) or reduce the need for both injections and office visits (in the case of treat-and-extend). (Tr. 831:6-837:8 (Albini); PTX 722.2-3 ("Dr. Brown: … I treat and extend from the start. I give 3 monthly injections and see them in 8 weeks."); DTX 2040.24; DTX 4113.8 ("In the 'treat-and-extend' approach … treatment is administered at each patient visit, even in the absence of macular edema. If the macula remains free of edema, and the vision is stable, the interval between visits is extended to a maximum of 10-11 weeks."); DTX 4194.13; DTX 3131.14 ("There are other strategies that may yield similar or even better VA outcomes and that require fewer visits. One such strategy is known as treat and extend, which is particularly appealing for use in routine clinical practice.");

DTX 3215.2 (treat and extend results in "fewer patient visits and treatments than monthly dosing"); see also DTX 204.4 (aflibercept PRN regimen reducing the need for monthly injections)). The existence and use of these prior art regimens, including regimens for aflibercept, also show that ophthalmologists had not failed in the development of regimens that could treat VEGF-related eye disorders while reducing injections and office visits.

Lastly, the Court finds that the blocking patents, which, as Dr. Albini explained, claimed subject matter that would have prevented anyone from developing and then using extended dosing regimens with aflibercept, also weigh in favor of a finding that there has not been a demonstrated failure of others in this case. (Tr. 850:21-852:14 (Albini); DTX 2062.105; DTX 2730.32; DTX 4116.32; DTX 4900.57; DDX 6.165-166). Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc., 903 F.3d 1310, 1341-42 (Fed. Cir. 2018).

"Evidence of unexpected results can be used to rebut a prima facie case of obviousness." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1369 (Fed. Cir. 2007). "The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995)

The law holds that a patentee must "show that the claimed invention exhibits some superior property or advantage that a

person of ordinary skill in the relevant art would have found surprising or unexpected" compared to the closest prior art. In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (cleaned up); see also Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014) ("To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention."); Alcon, Inc. v. Teva Pharms. USA, Inc., 664 F. Supp. 2d 443, 464 (D. Del. 2009) ("When 'unexpected' and 'significant' differences exist between the properties of the claimed invention and those of the prior art, a finding of nonobviousness may be warranted.") (relying on Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1378 (Fed. Cir. 2006)).

However, unexpected results also "do not necessarily guarantee that a new [product] is nonobvious." Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014). "While a 'marked superiority' in an expected property may be enough in some circumstances to render a [product] patentable, a mere difference in degree is insufficient." Id. (citation and internal quotation marks omitted).

Here, Dr. Csaky did not present any evidence that results for DME-DR using a regimen of 5 monthly injections followed by every-8-week dosing were unexpected. On claim 6, no evidence was presented on unexpected results, but the Court did receive some limited testimony from Dr. Csaky in the context of reasonable expectation of success, where oblique reference was made to "incredible results" from the VIEW AMD clinical trials. (Tr. 1867:2-15 (Csaky)). However, as Defendants observe, this discussion was not tied to the purportedly novel aspect of claim 6—isotonicity of the formulation—and there is little-to-no evidence of record with regard to any unexpected results stemming from the isotonicity of the Eylea formulation. The Court also received no evidence from Plaintiff as to the closest prior art, or what any unexpected results are being compared to, rendering Plaintiff's unexpected results assertions insufficient. Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014) ("To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art…").

In addition, when assessing unexpected results, any evidence that is in fact provided should be "weighed against contrary evidence indicating that the results were not unexpected or not a substantial improvement over the prior art." See Santarus, Inc. v.

Par Pharm., Inc., 720 F. Supp. 2d 427, 457 (D. Del. 2010), rev'd on other grounds, 694 F.3d 1344 (Fed. Cir. 2012) (relying upon In re Soni, 54 F.3d 746, 751 (Fed. Cir. 1995)). Here, for the results in general, as they relate to observations of visual acuity gains in the VIEW clinical trials, Dr. Albini testified as to the successes observed in the Phase 2 aflibercept AMD clinical trial, including the relatively few number of PRN injections required after the 4 monthly loading doses, and the long interval between the end of the initial doses and the first as-needed injection, pointing to a duration of action of aflibercept that would be expected to cover an 8-week interval. (Tr. 840:15-842:10 (Albini); DTX 204.4; DDX 6.150-154; see also Tr. 1977:7-1979:11 (Csaky); DTX 3173.6, 12-13, 19, 26, 28). Dr. Csaky did not contest or otherwise rebut the data reported for the aflibercept Phase 2 clinical trial.

In conclusion, the Court finds that Regeneron failed to demonstrate that any secondary considerations of non-obviousness overcome the showing of obviousness presented by Defendants.

IV. CONCLUSION

For the reasons discussed, the Court concludes as follows:

1. Regeneron has demonstrated by a preponderance of the evidence that the Defendants have infringed claims 4, 7, 9, 11, 14, 15, 16, and 17 of the '865 Patent;

2. Regeneron has demonstrated by a preponderance of the evidence that the Defendants will induce infringement of claims 6 and 25 of the '572 Patent and claims 11 and 19 of the '601 Patent;

3. Mylan has not demonstrated by clear and convincing evidence that claims 4, 7, 9, 11, 14, 15, 16, and 17 of the '865 Patent are anticipated or obvious in light of the prior art or invalid under 35 U.S.C. § 112 for lack of written description, lack of enablement, or indefiniteness.

4. Mylan has not demonstrated by clear and convincing evidence that claim 6 of the '572 Patent is invalid as anticipated;

5. Mylan has demonstrated by clear and convincing evidence that claim 6 of the '572 Patent is invalid as obvious;

6. Mylan has not demonstrated by clear and convincing evidence that claim 25 of the '572 patent is invalid as anticipated;

7. Mylan has demonstrated by clear and convincing evidence that claim 25 of the '572 patent is invalid as obvious;

8. Mylan has not demonstrated by clear and convincing evidence that Claim 11 of the '601 Patent is invalid as anticipated;

9. Mylan has demonstrated by clear and convincing evidence that Claim 11 of the '601 patent is invalid as obvious;

10. Mylan has demonstrated by clear and convincing evidence that Claim 19 of the '601 Patent is invalid as obvious; and

11. The Oral Motion for Judgment [ECF No. 548] is **DENIED.**

Out of an abundance of caution, the Court enters this Memorandum Opinion and Order under seal. The parties shall meet and confer to discuss which portions of this Memorandum Opinion can be unsealed. They shall submit a joint proposed redaction for the Court's review **on or before January 10, 2024.**

It is so **ORDERED.**

The Clerk is directed to transmit copies of both orders to counsel of record and to enter a separate judgment order.

DATED: December 27, 2023

Tom S Kleeh

THOMAS S. KLEEH, CHIEF JUDGE
NORTHERN DISTRICT OF WEST VIRGINIA