UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Inter Partes Review No.: IPR2021-00881

U.S. Patent No. 9,254,338 B2
Filed: July 12, 2013
Issued: February 9, 2016
Inventor: George D. Yancopoulos

Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,254,338 B2

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1003	Expert Declaration of Mary Gerritsen, Ph.D. in Support of Petition for *Inter Partes* Review of U.S. Patent No. 9,254,338 B2, dated Apr. 26, 2021 ("Gerritsen")
1004	Jocelyn Holash et al., *VEGF-Trap: A VEGF Blocker with Potent Antitumor Effects*, 99 PROC. NAT'L ACAD. SCI. 11393 (2002) ("Holash")
1005	Quan Dong Nguyen et al., *A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration*, 116 OPHTHALMOLOGY 2141 (2009) ("Nguyen-2009")
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1083	Nucleotide sequence alignment of SEQ ID NO:1 of the '069 patent with SEQ ID NO:15 of the '758 patent and SEQ ID NO:3 of Dix ("'069 Nucleotide Sequences")
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1091	EYLEA® Prescribing Information ("Eylea PI")
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1093	Amino acid sequence alignment of SEQ ID NO:2 of the '338 patent with SEQ ID NO:16 of the '758 patent and SEQ ID NO:4 of Dix ("'338 Amino Acid Sequences")
1094	Nucleotide sequence alignment of SEQ ID NO:1 of the '338 patent with SEQ ID NO:15 of the '758 patent and SEQ ID NO:3 of Dix ("'338 Nucleotide Sequences")

Mylan Pharmaceuticals Inc. ("Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. §§ 42 *et seq*., seeking cancellation of claims 1, 3-11, 13-14, 16-24, and 26 (the "Challenged Claims") of U.S. Patent No. 9,254,338 ("'338 patent") (Ex.1001), assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron" or "Patent Owner").

I. INTRODUCTION.

The Challenged Claims should have never issued. They are drawn to "VEGF Trap-Eye" dosing regimens known to persons of ordinary skill in the art (hereafter, "skilled artisans") long before the patent's alleged 2011 priority date. Regeneron's age-related macular degeneration ("AMD") clinical trials (VIEW1/VIEW2) with EYLEA® (a/k/a VEGF Trap-Eye or aflibercept) were designed to use the precise dosing regimens now covered by the Challenged Claims. The problem: Regeneron publicly disclosed these exact dosing regimens to skilled artisans as early as 2008, three years prior to filing its patent application. Regeneron then withheld those publications from the Examiner, allowing the '338 patent to issue. For at least these reasons, the Challenged Claims are unpatentable.

Petitioner thus files this Petition, supported by expert declarations from Dr. Thomas Albini—a renowned ophthalmologist (Ex.1002), and Dr. Mary Gerritsen—a pharmacologist with over thirty years' experience (Ex.1003).

Anticipation. Each Challenged Claim is anticipated. VEGF Trap-Eye was a

known blocker of vascular endothelial growth factor ("VEGF") independently disclosed in the scientific literature, (*see* Ex.1004, Holash; Ex.1005, Nguyen-2009; Ex.1006, Dixon; Ex.1007, Adis) and patented (*see* Ex.1008, '173 patent; Ex.1009, '664 patent; Ex.1010, '758 patent) well before the alleged priority date.

At least two VEGF Trap-Eye clinical trials—"VIEW1" and "VIEW2" and the dosing regimens used therein—were widely published in numerous, fully-enabled prior art references, by Regeneron and others, years before the alleged priority date. These publications disclosed *all* of the elements of the dosing regimen(s) claimed in the '338 patent—including administering three monthly loading doses of VEGF Trap-Eye, followed by additional bi-monthly doses—and were published in numerous, fully-enabled prior art references.

Obviousness. The claimed methods also would have been obvious. VEGF Trap-Eye nucleotide and amino acid sequences were patented and widely disclosed to skilled artisans. The prior art further demonstrates the frequency and financial burden of monthly intravitreal injections—recognized concerns with traditional dosing regimens for angiogenic eye disorders (Ex.1006, Dixon, 1574), motivating the skilled artisan to pursue less frequent dosing schedules compared to the monthly dosing often used for other anti-VEGF therapeutics. Regeneron itself (among others) placed into the public domain—as early as 2008—one such dosing regimen. (*See, e.g.*, Ex.1006, Dixon, 5; Ex.1007, Adis, 268; Ex.1014, NCT-795; Ex.1015,

NCT-377; Ex.1013, Regeneron (8-May-2008)). Combined with the abundance of positive, prior art data from Regeneron's clinical trials, a skilled artisan would have reasonably expected success at treating angiogenic eye disorders with the claimed dosing regimens.

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

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

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

Viatris Inc. and Mylan Inc. are parent companies of Petitioner Mylan Pharmaceuticals Inc. Accordingly, Viatris Inc., Mylan Inc., and Mylan Pharmaceuticals Inc. are identified as real parties-in-interest to the current Petition. Momenta Pharmaceuticals, Inc. is a wholly-owned subsidiary of Johnson & Johnson, a publicly held company. Momenta Pharmaceuticals, Inc. and Johnson & Johnson are also real parties-in-interest to the current Petition. No other parties exercised or could have exercised control over this Petition; no other parties funded, directed and controlled this Petition. *See* Trial Practice Guide, 77 Fed. Reg. 48759-60 (Aug. 14, 2021).

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

Petitioner identifies *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, No. IPR2021-00880 (P.T.A.B.), filed concurrently herewith. To the best of Petitioner's knowledge, there are no other judicial or administrative matters that would affect, or

be affected by, a decision in this proceeding; nonetheless, out of an abundance of caution, Petitioner further identifies *Chengdu Kanghong Biotechnology Co. v. Regeneron Pharms., Inc.*, No. PGR2021-00035 (P.T.A.B.).

U.S. Patent Nos. 9,669,069 B2, 10,130,681 B2, 10,857,205 B2, 10,828,345 B2, and 10,888,601; and U.S. Patent Application Nos. 17/072,417, 17/112,063, and 17/112,404 claim the benefit of the '338 patent filing date.

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

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

Lead	Back-Up
Paul J. Molino (Reg. No. 45,350) paul@rmmslegal.com <u>Postal and Hand Delivery Address</u> Rakoczy Molino Mazzochi Siwik LLP 6 West Hubbard Street Chicago, IL 60654 Telephone: (312) 222-6300 Facsimile: (312) 843-6260 *Petitioner consents to email service at:* MYL_REG_IPR@rmmslegal.com	William A. Rakoczy (*pro hac vice* to be filed) wrakoczy@rmmslegal.com Heinz J. Salmen (*pro hac vice* to be filed) hsalmen@rmmslegal.com Neil B. McLaughlin (Reg. No. 70,810) nmclaughlin@rmmslegal.com <u>Postal and Hand Delivery Address</u> Rakoczy Molino Mazzochi Siwik LLP 6 West Hubbard Street Chicago, IL 60654 Telephone: (312) 222-5127 Facsimile: (312) 843-6260

Please direct all correspondence to lead and back-up counsel at the contact information above. Petitioner also consents to service by email at: MYL_REG_IPR@rmmslegal.com. Petitioner intends to file a motion seeking the admission of William A. Rakoczy and Heinz J. Salmen to appear *pro hac vice* when authorized to do so.

III. PAYMENT UNDER 37 C.F.R. § 42.15(a) AND § 42.103.

The required fees are submitted herewith. The undersigned representative of Petitioner hereby authorizes the Patent Office to charge any additional fees or credit any overpayment to Deposit Account 503626.

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

Petitioner certifies that the '338 patent—which issued on February 9, 2016—is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging any claim thereof on the grounds identified herein. Neither Petitioner nor any other real party-in-interest has filed a civil action challenging the validity, or been served with a complaint alleging infringement, of the '338 patent, more than one year prior to the filing of this Petition. *See Motorola Mobility LLC v. Arnouse*, No. IPR2013-00010, 2013 WL 12349001, *3 (P.T.A.B. Jan. 30, 2013).

V. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW.

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

VI. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED.

A. CHALLENGED CLAIMS.

Petitioner requests IPR of claims 1, 3-11, 13-14, 16-24, and 26 of the '338 patent, and cancellation of these claims as unpatentable.

B. STATUTORY GROUNDS OF CHALLENGE.

Each of the following prior art references anticipate the Challenged Claims:

Ground	Proposed Rejections Under 35 U.S.C. § 102
1	Dixon
2	Adis
3	Regeneron (8-May-2008)
4	NCT-795
5	NCT-377

In addition, at least the following render the Challenged Claims obvious:

Ground	Proposed Rejections Under 35 U.S.C. § 103
6	Dixon alone or in view of the '758 patent and/or Dix

Petitioner's full statement of reasons for the relief requested is set forth in greater detail below, and in the supporting declarations of Drs. Albini and Gerritsen.

VII. OVERVIEW OF THE '338 PATENT.

A. THE '338 PATENT.[1]

The '338 patent confirms that angiogenic eye disorders, such as AMD, diabetic macular edema ("DME"), and retinal vein occlusion ("RVO") were known to be effectively treated through vascular endothelial growth factor ("VEGF")[2] inhibition. (Ex.1001, '338 patent, 1:24-52). Indeed, prior to the '338 patent priority date, ranibizumab (LUCENTIS®), an anti-VEGF antibody fragment marketed by Genentech, was FDA-approved for monthly administration via intravitreal injection to treat angiogenic eye disorders, including AMD. (*Id.*, 1:49-52; *see also* Ex.1048,

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[1] Solely for purposes of this IPR, Petitioner assumes a January 13, 2011 priority date. However, Petitioner reserves all rights to challenge the extent to which Regeneron asserts application of pre-AIA standards of patentability. The '338 patent is subject to the AIA given the inclusion of new matter in the Continuation-In-Part Application No. 13/940,370, filed July 12, 2013.

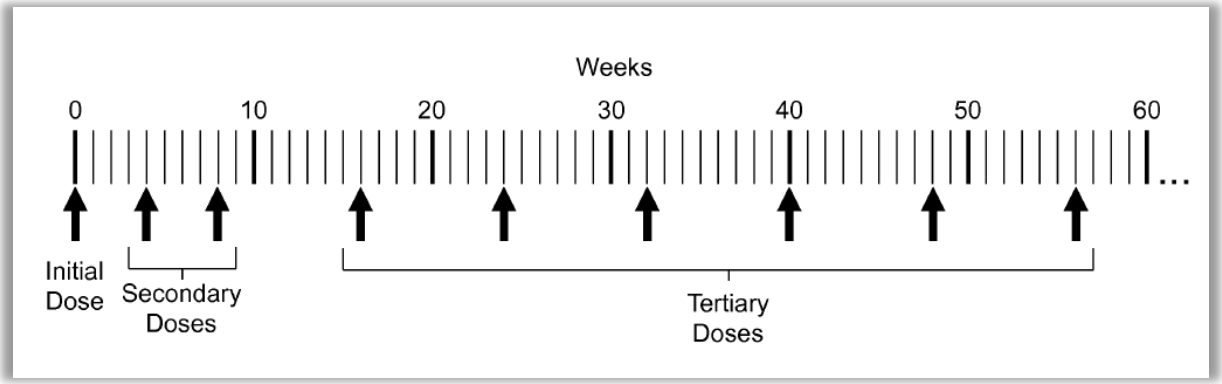
[2] Vascular endothelial growth factor (VEGF) is a "naturally occurring glycoprotein in the body that acts as a growth factor for endothelial cells." (Ex.1011, Semeraro, 711). Early research linked activity of VEGF-A to the development of ocular diseases such as neovascular AMD. (Ex.1043, Brown, 627-28).

Lucentis, 1). The ’338 patent asserts a need in the art for regimens that allow less frequent dosing. (Ex.1001, ’338 patent, 1:53-59).

The ’338 patent broadly claims dosing regimens for treating angiogenic eye disorders, including AMD, via: **(1)** administering a single initial dose of a VEGF antagonist (VEGF Trap-Eye), followed by **(2)** one or more “secondary doses” administered two to four weeks after the immediately preceding dose, followed **(3)** by one or more “tertiary doses” administered at least eight weeks apart. (*See, e.g., id.*, 23:2-18 (Claim 1)). The ’338 patent also specifically claims the prior art VIEW1/VIEW2 regimen, which eventually became the FDA-approved regimen for EYLEA® (i.e., VEGF Trap-Eye/aflibercept):

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

(*Id.*, 3:57-64; *id.*, 23:23-28, 24:20-25). This VIEW1/VIEW2 dosing regimen is described as “an exemplary dosing regimen of the present invention” and is depicted graphically by Figure 1 of the ’338 patent:



(*Id.*, (Fig.1); *see also id.*, 3:66-67; *id.*, 2:54-60). Figure 1 illustrates and exemplifies a dosing regimen falling within the Challenged Claims.

During prosecution, Regeneron argued, in response to double-patenting rejections, the (then-pending) Challenged Claims were patentably distinct from its Monthly-Dosing Patents[3] on the ground that those prior patents did not disclose the exact regimen specified in the pending claims. (Ex.1017, '338 FH, 9/11/2015 Response, 6). Regeneron further argued once-per-month dosing represented the standard of care and that the Challenged Claims were distinct because an infinite

[3] Regeneron's "Monthly-Dosing Patents" refers to U.S. Patent Nos. 7,303,746; 7,303,747; 7,306,799; and 7,521,049; which generally disclose doses separated by at least two weeks. (Ex.1016, Monthly-Dosing Patents; Ex.1017, '338 FH, 6/23/15 Office Action, 5-9).

number of other treatment protocols could have been considered. (*Id.*, 6-9; Ex.1018, Heier-2012, 2537).

Regeneron notably told the Examiner that Example 5 "illustrates an administration regimen encompassed by [issued claims 1 and 14] (*i.e.*, 3 initial doses of VEGF Trap administered once every four weeks, followed by additional doses administered once every 8 weeks) for the effective treatment of diabetic macular edema (DME)." (*See* Ex.1017, '338 FH, 9/11/2015 Response, 8). One Example 5 dosing regimen is identical to the VIEW1/VIEW2 regimen for AMD that was publicly disclosed years before the '338 patent filing.

B. EUROPEAN EQUIVALENT, EP-325.

EP-325 (Ex.1062)—Regeneron's then co-pending equivalent—included claims identical in scope to the Challenged Claims; however, EP-325 never issued and was abandoned. (*Compare* EP-325, Claims 1 and 11 (Ex.1063, EP-325-FH, 1/23/2012 Original Application, 19-22), *with* '338 patent, Claim 1 (Ex.1001, '338 patent, 23:2-18); *compare* EP-325 Claim 31 (Ex.1062, 21 (identifying the "VEGF receptor-based chimeric molecule" by its amino acid sequence), *with* '338 patent, Claim 14 (Ex.1001, '338 patent, 24:3-15 (same))). The EPO Examiner rejected the EP-325 claims for, *inter alia*, lacking novelty/inventive step over several prior art references, including those disclosing aflibercept (i.e., VEGF Trap-Eye) as an anti-angiogenesis agent (e.g., Wiegand (Ex.1084)); prior art ranibizumab (LUCENTIS®)

dosing regimens (e.g., Shams (Ex.1085)); and prior art VEGF Trap-Eye dosing regimens (e.g., Regeneron Sept. 28, 2008 Press Release (Ex.1056)). (*See* Ex.1063, EP-325-FH, 8/21/2014 Communication, 3-8).

Regeneron tried narrowing the EP-325 claims to avoid the rejections (*id.*, 12/17/2014 Amendment, 19); but the EPO Examiner—as well as third party observers—responded with additional prior art, including, *inter alia* Regeneron Press Releases, a 2008 conference slide presentation, a VIEW2 record from ClinicalTrials.gov, and Dixon (Ex.1006). (*Id.*, 9/5/2016 Observations, 2-8; *id.*, 9/7/2016 Observations, 2-8; *id.*, 1/3/2017 Communication, 1-8). Consequently, Regeneron abandoned EP-325. (*Id.*, 6/5/2017 Withdrawal).

Regeneron never cited the EP-325 prior art references discussed above to the '338 patent Examiner.

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

In accordance with 37 C.F.R. § 42.100(b), the Challenged Claims must be "construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b)," i.e., the *Phillips* standard. 83 Fed. Reg. 197, 51340-51359 (Oct. 11, 2018); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). Petitioner and expert declarant, Dr. Albini, have applied this standard.

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

The Challenged Claims recite the phrases "initial dose," "secondary dose," and "tertiary dose." A skilled artisan would understand each as expressly defined in the '338 patent specification:

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

(Ex.1001, '338 patent, 3:31-45 (emphasis added); Ex.1002, Albini ¶ 41). The specification further explains that "the immediately preceding dose" means "in a sequence of multiple administrations, the dose of VEGF antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses." (Ex.1001, '338 patent, 3:51-56; Ex.1002, Albini ¶ 41). Petitioner proposes that each claim term be construed consistent with these express definitions: "initial dose" means "the dose which is administered at the beginning of the treatment regimen"; "secondary dose(s)" means "the dose(s) which

are administered after the initial dose"; and "tertiary dose(s)" means "the dose(s) which are administered after the secondary dose(s)."

1. Regeneron's contradictory construction for "tertiary dose," if presented here, must be rejected.

To the extent Regeneron proposes a construction for "tertiary dose" that is consistent with its proposal in the '345 Patent PGR—i.e., as "dose(s) that maintain(s) a therapeutic effect throughout the course of treatment," (PO's Preliminary Response, *Chengdu Kanghong Biotechnology Co. v. Regeneron Pharms., Inc.*, No. PGR2021-00035, 9 (P.T.A.B. Apr. 15, 2021) ("'345 Patent PGR")—it should be rejected for at least the following reasons.

First and foremost, as described above, the '338 patent specification recites an *express* definition that provides the patentees' intended meaning to the claims: "the 'tertiary doses' are the doses which are administered after the secondary doses." (Ex.1001, '338 patent, 3:36-38). The claim term is "set off by quotation marks," which "[is] often a strong indication that what follows is a definition" and "the patentee must be bound by the express definition." *Sinorgchem Co., Shandong v. Int'l Trade Comm'n*, 511 F.3d 1132, 1136 (Fed. Cir. 2007). In other words, the express definition of "tertiary dose" is "clearly, deliberately, and precisely defined," *id.*, in the '338 patent—nothing more is needed to understand the term and there is no basis for straying from that express definition.

Second, Regeneron's proposed construction is unsupported and the intrinsic

record does not suggest reading-in limitations. *Phillips*, 415 F.3d at 1323 (affirming the general prohibition against reading limitations from the specification into the claims). For example, Regeneron relies exclusively on column 2 as purported support for its narrowed construction ('345 Patent PGR, 11), but that specification passage only describes a single embodiment, i.e., bi-monthly dosing.[4] By comparison, the *express* definition recited in the specification (i.e., "doses which are administered after the secondary doses") provides the exact temporal and sequential

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[4] Regeneron's proposed construction for "tertiary doses" also is in conflict with the plain language of the '338 patent claims, which require "tertiary doses" administered "at least 8 weeks after the immediately preceding dose" *irrespective* of whether the injection "maintain[s] a therapeutic effect." (*See* Ex.1001, '338 patent, Claims 1, 17). Consequently, the '338 patent—which derives from the same parent application as the Chengdu-challenged '345 Patent—would improperly require a different construction of "tertiary dose" for those claims to have meaning, further illustrating the extent to which Regeneron's proposed construction, if presented in this IPR, would inject indefiniteness into the claims. *Samsung Elecs. Co. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1378 (Fed. Cir. 2019) ("Where multiple patents derive from the same parent application and share many common terms, we must interpret the claims consistently across all asserted patents.").

distinction from the other doses in the regimen that the patent drafters envisioned for all claimed dosing regimens. (Ex.1001, '338 patent, 3:31-38 ("The terms . . . refer to the temporal sequence of administration."); *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so."). No further construction is necessary. *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998) ("When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term.")).

Third, Regeneron's proposal improperly injects ambiguity and indefiniteness where there is none. *Ruckus Wireless, Inc. v. Innovative Wireless Sols., LLC*, 824 F.3d 999, 1004 (Fed. Cir. 2016) (rejecting a construction encompassing subject matter that would render the claims invalid under § 112). Stated another way, Regeneron's proposed construction, itself, requires construction. Specifically, the terms "maintain," "therapeutic effect," and "throughout the course of treatment" lack both definition and plain and ordinary meaning. A skilled artisan is therefore left wondering what Regeneron's construction is supposed to mean, as well as what metrics one is supposed to use to assess each imported limitation.

Finally, Regeneron notably ignores construing "initial" and "secondary." Consequently, a skilled artisan, under Regeneron's proposal, is uncertain whether

those terms carry "therapeutic effect" limitations as well or whether the specification's express definitions apply—adding further uncertainty and ambiguity to the Challenged Claims. Petitioner's proposal to apply the express definitions for all three terms, on the other hand, is clear to a skilled artisan and free of such problems.

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

"4 weeks." A skilled artisan would understand the phrase "4 weeks"—as it appears in the Challenged Claims—to be synonymous with monthly administration. (Ex.1002, Albini ¶ 42; Ex.1001, '338 patent, 7:54-56 ("'[M]onthly' dosing is equivalent to dosing once every four weeks."); *id.*, 14:41-52 (patients received "monthly injections" which "means patients who received . . . injections once every four weeks")).

"8 weeks." A skilled artisan would similarly understand the phrase "8 weeks"—as it appears in the Challenged Claims—to be synonymous with bi-monthly (or every-other-month administration). (Ex.1001, '338 patent, 7:54-56; *id.*, 14:41-52; Ex.1002, Albini ¶ 42).

C. "VEGFR1 COMPONENT," "VEGFR2 COMPONENT" AND THE "MULTIMERIZATION COMPONENT."

Claim 1 of the '338 patent recites that the "VEGF antagonist" comprises a "VEGFR1 component," a "VEGFR2 component," and a "multimerization

component." According to the '338 patent, these terms all refer to separate amino acid domains of "SEQ ID NO:2." A skilled artisan would understand these terms to collectively refer to aflibercept (a/k/a VEGF Trap or VEGF Trap-Eye or VEGFR1R2-FcΔC1(a)). (Ex.1001, '338 patent, 2:32-37; Ex.1002, Albini ¶ 44).

D. "TREATING."

1. The "method for treating" element of the preamble is not a limitation of the Challenged Claims, and therefore does not require construction.

The "method for treating" preamble of independent claims 1 and 14 is "merely a statement of purpose or intended use" for the claimed dosing regimen(s) and is non-limiting. *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001); *Vizio, Inc. v. Int'l Trade Comm'n*, 605 F.3d 1330, 1340-41 (Fed. Cir. 2010); *Arctic Cat Inc. v. GEP Power Prods., Inc.*, 919 F.3d 1320, 1327 (Fed. Cir. 2019) ("as a general rule preamble language is not treated as limiting")). Indeed, "method for treating"—like the "method" preamble in *Bio-Rad*—neither provides antecedent basis for any other claim element[5] nor gives life, meaning or vitality to the claimed dosing regimen, and thus, it is not a limitation. *Bio-Rad Lab'ys, Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1371 (Fed. Cir. 2020) (citing *TomTom, Inc. v. Adolph*, 790 F.3d 1315, 1322-25 (Fed. Cir. 2015)) ("In

[5] "Treating" (or any form of "treat") appears nowhere else in any of the claims.

TomTom . . . [t]he two-part preamble of the asserted claim recited: '[1] [a] method for generating and updating data [2] for use in a destination tracking system of at least one mobile unit comprising . . . . We held that the first part of the preamble, 'method for generating and updating data,' was not limiting and did not provide an antecedent basis for any claim terms. We also found that the term did not recite essential structure or steps, or give necessary life, meaning, and vitality to the claim; rather, it stated 'a purpose or intended use.'" (citations omitted)); *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (preamble was non-limiting where it "does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims"). Nothing in the intrinsic record here suggests otherwise. For example, there is no evidence that Regeneron asserted the "method for treating" preamble to traverse any Examiner rejections. Instead, Regeneron relied on the dosing frequencies required in the Challenged Claims to purportedly distinguish the prior art, "standard of care." (*See, e.g.*, Ex.1017, '338 FH, 9/11/15 Remarks, 6-9).

Moreover, Regeneron is foreclosed by Federal Circuit precedent from arguing that its reliance on alleged "unexpected results' during prosecution demonstrates that efficacy is a necessary feature of the claimed method. *Purdue Pharma L.P. v. Endo Pharms. Inc.*, 438 F.3d 1123, 1136-37 (Fed. Cir. 2006) (en banc) (holding that patentee's reliance on its "surprising discovery" of the four-fold dosage range to

distinguish its oxycodone formulation from the prior art did not make the four-fold range a necessary feature of the claimed formulations). The Board has also rejected similar arguments. *Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, No. IPR2016-00712, 2016 WL 5753968, *5 (P.T.A.B. Sept. 22, 2016) (holding that "method of treating a patient" preamble was non-limiting despite patentee's reliance on "surprising and unexpected" clinical results of efficacy to distinguish the claimed invention from the prior art).

For these reasons, Petitioner submits that the preamble is non-limiting and no construction of "treating" is necessary to ascertain the scope of the Challenged Claims.

2. Regeneron's anticipated argument that the "method for treating" preamble is a positive limitation should be rejected.

In the '345 Patent PGR, Regeneron has asserted that an analogous "method for treating" preamble is a positive claim limitation requiring a therapeutically effective method for treatment. ('345 Patent PGR, 7-9). To the extent Regeneron raises the same argument here, it should be rejected. First, the "method for treating an angiogenic eye disorder" phrase has no bearing on the dosing steps in the claim, because "the steps . . . are performed in the same way regardless whether or not the patient experiences" treatment of their angiogenic eye disorder. *Bristol-Myers*, 246 F.3d at 1375. (Ex.1001, '338 patent, 13:3-17 (Table 1) (showing that almost 5% of the patients in the 2Q8 arm failed to maintain vision)). In other words, the preamble

is merely a statement of the *intended* purpose for the claimed regimen, and therefore, is not a limitation. *Bristol-Myers*, 246 F.3d at 1375; *Copaxone*, 906 F.3d at 1022-23.

Second, as stated above, "method for treating" provides no antecedent basis for any other claim element, and any argument that the claim terms "the patient" and "angiogenic eye disorders" find their respective meaning in the preamble is meritless. Like in *Copaxone*, these terms do not "change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims." *Copaxone*, 906 F.3d at 1023. Instead, the claimed dosing regimen stays the same. Consequently, neither the "method for treating" element nor the "angiogenic eye disorder in a patient" element in the two-part preamble rise to the level of a positive claim limitation.

Third, even if the Board finds the preamble limiting, the claimed method is not *required*—as Regeneron argues—to be therapeutically effective. Instead, to the extent the preamble is limiting, it is "a statement of the intentional purpose for which the method must be performed." *GlaxoSmithKline LLC v. Glenmark Pharms., Inc.*, No. 14-877-LPS-CJB, 2016 WL 3186657, at *7 (D. Del. June 3, 2016). In other words, to anticipate the claims, it is enough that the prior art's "intentional purpose" is to treat an angiogenic eye disorder—showing actual therapeutic effectiveness is not required.

For at least the above reasons, Petitioner submits that no construction of "treating" is necessary to ascertain the scope of the Challenged Claims.

3. If construed to be a limitation, the preamble's plain and ordinary meaning—which does not provide any specific efficacy requirement—must govern.

If the Board determines that the claim language requires construction, or that the preamble is a limitation, the patent does not provide a definition or any metric for what constitutes "treating" an angiogenic eye disorder within the context of the Challenged Claims. Given this absence of lexicography, a person of ordinary skill in the art would apply the term's plain and ordinary meaning: administering a therapeutic to a patient, without a specific degree of efficacy required. (Ex.1002, Albini ¶ 43).

In the event Regeneron attempts to equate "efficacy" with "treating" (which, at the outset, is impermissible under Federal Circuit precedent, *see Phillips*, 415 F.3d at 1323), the Challenged Claims are still unpatentable for the reasons set forth herein. Specifically, "efficacy" in the context of the '338 patent only requires that the patient exhibit a loss of fifteen or fewer letters on the Early Treatment Diabetic Retinopathy Study ("ETDRS") visual acuity chart within 104 weeks of treatment initiation. (*See, e.g.*, Ex.1001, '338 patent, 7:15-32; Ex.1002, Albini ¶ 43). Even the "certain embodiments" efficacy metric requires only a gain of one or more ETDRS letters within 104 weeks. Applied to the claims, efficacy far exceeding this *de minimis*

level were indisputably disclosed in prior art using VEGF Trap-Eye dosing regimens that involved fewer doses than the every-8-week regimen. (*See, e.g.*, Ex.1020, Heier-2009, 45 (reporting mean improvements in BCVA of 9.0 letters from baseline after "three monthly doses (2.0 mg) followed by as-needed dosing); *id.* ("patients received a mean 3.5 injections" over 15-month *pro re nata* (PRN) (i.e., as-needed dosing) phase)).

IX. PERSON OF ORDINARY SKILL IN THE ART.

A skilled artisan is presumed to be aware of all pertinent art, think along the lines of conventional wisdom, and possess common sense and ordinary creativity in the pertinent field. A skilled artisan here would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists. (Ex.1002, Albini ¶¶ 26-28; Ex.1003, Gerritsen ¶¶ 20-24).

X. THE SCOPE AND CONTENT OF THE PRIOR ART.

The publications below reflect anticipatory disclosures of the subject matter in the Challenged Claims, together with knowledge that skilled artisans would bring to bear in reading the prior art at the time of the invention, i.e., January 13, 2011. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367-68 (Fed. Cir. 2015). As established in *KSR*, the knowledge of a skilled artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-22 (2007).

A. VEGF TRAP-EYE/AFLIBERCEPT BACKGROUND.

Aflibercept is an engineered prior art fusion protein consisting of domain 2 of the human VEGF receptor 1 (VEGFR1); domain 3 of the human VEGF receptor 2 (VEGFR2); fused to the Fc portion of human IgG_1. (*See* Ex.1004, Holash, 11394 (Fig.1A)). Aflibercept, VEGF Trap, VEGF Trap-Eye, VEGF-$Trap_{R1R2}$, and AVE0005 are simply different names for the same molecule. (*See, e.g.*, Ex.1006, Dixon, 1575 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure . . . ."); Ex.1021, 2009 10-Q, 20 ("VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications."); *see also id.*, 27).

VEGF Trap-Eye was developed to target angiogenic disorders, including eye disorders, such as AMD, DME, and RVO. Earlier generation therapeutics targeted specifically at blocking VEGF included ranibizumab (LUCENTIS®) and bevacizumab (AVASTIN®), both monoclonal antibodies, which bind to, and thus inhibit the activity of, VEGF-A. However, the FDA-approved monthly-dosing regimen for ranibizumab was costly and inconvenient, leading researchers to: (1) investigate less-frequent dosing regimens, and (2) focus on new drugs with extended duration of action. (Ex.1006, Dixon, 1574; Ex.1002, Albini ¶¶ 54-62). One such drug was VEGF Trap-Eye, described by Holash in 2002. (Albini ¶¶ 63-70). At the time, LUCENTIS® approved indications overlapped those Regeneron was exploring for EYLEA®. Both are VEGF antagonists.

The identity of VEGF Trap-Eye/aflibercept was readily disclosed in the prior art. (*See e.g.*, Ex.1007, Adis, 261; Ex.1006, Dixon, 1575). The amino acid and nucleic acid sequences also were widely disclosed. (*See, e.g.*, Ex.1022, '757 patent, SEQ ID NO:16, Fig.24A-C; Ex.1010, '758 patent, SEQ ID NO:16, Fig.24A-C; Ex.1023, '959 patent, Fig.24A-C; Ex.1024, '758 FH, 12/22/2011 PTE, 2, 6-7; Ex.1002, Albini, ¶ 44). Thus, the molecular structure and sequence for aflibercept was not only known to the skilled artisan, but also would have been an inherent

aspect of each of the prior art references that disclose VEGF Trap-Eye/aflibercept.[6] *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380 (Fed. Cir. 2002) ("Under the doctrine of inherency, if [a claim] element is not expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element 'is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'"). VEGF Trap-Eye was placed into clinical studies in the mid-2000's. (Ex.1005, Nguyen-2009, 2147 (reporting from Phase 1 study that "a single intraocular injection . . . appears safe and well tolerated" and that there were "substantial effects after single injections of 1.0 to 4.0 mg."). In 2008, Regeneron publicly announced its Phase 2 trial, CLEAR-IT-2, assessing PRN dosing after 4 monthly loading doses, followed by Phase 3 testing that included a treatment arm of 3 monthly injections followed by every-8-week dosing (Ex.1006, Dixon, 1576; Ex.1002, Albini ¶ 71)—the precise dosing regimen Regeneron claimed in the '338 patent application filed *almost three years later*.

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[6] For the Challenged Claims, the sequences set forth in claims 1 and 14, respectively, represent the amino acid and nucleotide sequences for aflibercept that were well known and disclosed in the prior art. (*See, e.g.*, Ex.1004, Holash, 11395; Ex.1010, '758 patent, Fig.24A-C; Ex.1008, '173 patent, SEQ ID NO:2; Ex.1002, Albini ¶44).

B. PETITIONER'S PRIOR ART REFERENCES.[7]

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

Trial	Name	Reference(s)	Dosage Regimen
Phase 1 (AMD)	CLEAR-IT-1	Dixon; Nguyen	Single dose (0.5, 2, and 4 mg)
Phase 2 (AMD)	CLEAR-IT-2	Dixon; Adis; Heier-2009	Monthly or quarterly doses through wk-12, followed by PRN (0.5, 2, and 4 mg)
Phase 3 (AMD)	VIEW1; VIEW2	Dixon; Adis; NCT-795 NCT-377; Regeneron (8-May-2008)[8]	Three monthly doses, followed by bi-monthly doses (2 mg)

[7] The asserted prior art references all qualify as publications that were available to—and indeed cited by—interested, skilled artisans before the '338 patent's earliest, purported priority date (i.e., January 13, 2011). (Ex.1003, Gerritsen ¶¶49, 56, 64, 75, 78, 79, 82-89; Ex.1006, 1579 (citing NCT Studies); Ex.1007, Adis, 268 (citing

As described in more detail below, the dosing regimen disclosed in the aforementioned Phase 3 trials involved an "initial dose" at day 0; two "secondary doses" administered at weeks 4 and 8; followed by "tertiary doses" administered every eight weeks after the preceding dose (i.e., weeks 16, 24, 32, 40, etc.). (Ex.1002, Albini ¶¶ 71, 126, 172-75, 218-20, 267-68, 315-17).

1. Dixon (Ex.1006).

Dixon published in 2009 and thus constitutes prior art under 35 U.S.C. § 102. Regeneron has confirmed that "Dixon was publicly accessible in print by October 2009, and online by August 20, 2009." (*See* Petition for IPR of U.S. Patent No. 9,220,631, *Regeneron Pharms., Inc. v. Novartis Pharma AG*, IPR2021-00816, Paper No. 1, 23 (Apr. 16, 2021)). To Petitioner's knowledge, Regeneron did not submit Dixon during prosecution leading to the '338 patent and it was never considered by the Examiner. (*See* Ex.1001, '338 patent, References Cited). In fact, *none* of the numerous pre-2011 publications disclosing the VIEW1/VIEW2 dosing regimens (e.g., Regeneron press releases, SEC filings, ClinicalTrials.gov submissions) were

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Regeneron Press Releases)).

[8] The VIEW1/VIEW2 trials were discussed in numerous Regeneron and Bayer press releases before the '338 patent priority applications were filed in 2011. (*See, e.g.*, Ex.1013, Regeneron (8-May-2008)).

submitted to or cited by the Examiner during prosecution. Dixon was cited, however, during prosecution of EP-325 against substantively identical claims (*see supra* § VII(B), above), confirming Regeneron's knowledge of Dixon and its relevance to the claimed dosing regimen. (Ex.1063, EP-325-FH, 9/5/2016 Observations, 2 (Ref. OBS5); *id*., 1/3/2017 Communication, 4 (same)). Dixon also expressly incorporates by reference NCT-795 and NCT-377 (discussed below). (Ex.1006, Dixon, 1579 (Bibliography Nos. 46-47)). *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("Incorporation by reference provides a method for integrating material from various documents into a host document—a patent or printed publication in an anticipation determination.").

Dixon teaches that VEGF Trap-Eye is an "anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Ex.1006, Dixon, 1573). Dixon also discloses details regarding Phase 3 trials (VIEW1/VIEW2) and the dosing regimens used therein. (*Id.*, 1573, 1575-76, 1579 (Bibliography Nos. 46-47); Ex.1002, Albini ¶¶ 74-82; Ex.1003, Gerritsen ¶ 87). Dixon notes the "time and financial burden of monthly injections" led researchers "to examine the efficacy of alternative dosing schedules." (Ex.1006, Dixon, 1574). Identifying the problem of the "significant time and financial burden [that] falls on patients during their treatment course" of monthly injections of drugs

such as ranibizumab, and the desirability of "decreased dosing intervals," Dixon reports that "[t]he development of new drugs for neovascular AMD has thus focused on both improving efficacy and extending duration of action." (Ex.1006, Dixon, 1574, 1577; Ex.1002, Albini ¶¶ 76-77).

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

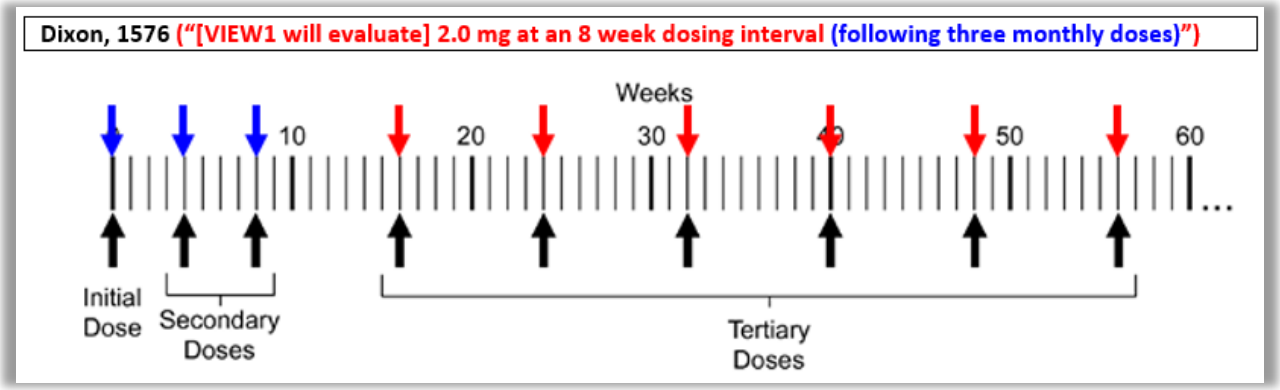

Figure 1. (Modified from Fig.1 of the '338 patent).

Dixon's disclosure of an "8 week dosing interval (following three monthly doses)," means that three monthly doses (**blue arrows**) were to be administered, followed by injections at eight week intervals thereafter (**red arrows**). (*See* Ex.1006, Dixon, 1576; Ex.1002, Albini ¶ 80).

Dixon also discloses the promising results of the Phase 2 CLEAR-IT-2 study of VEGF Trap-Eye in AMD, reporting that patients treated with four monthly loading doses of VEGF Trap-Eye (2.0 mg) followed by PRN dosing exhibited mean

improvement in visual acuity of nine letters and a mean decrease in retinal thickness of 143 µm. (Ex.1006, Dixon, 1576; Ex.1002, Albini ¶¶ 78-79).

2. Adis (Ex.1007).

Adis published in 2008 and thus constitutes prior art under 35 U.S.C. § 102. To Petitioner's knowledge, Adis was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, '338 patent, References Cited).

Adis discloses, *inter alia*, VEGF treatment to prevent blood vessel formation and vascular leakage associated with wet AMD. (Ex.1007, Adis, 261). Adis further teaches that "Regeneron and Bayer are developing [aflibercept] for eye disorders." (*Id.*; Ex.1002, Albini ¶ 84).

Adis discusses Regeneron's VIEW2 study to evaluate the safety and efficacy of aflibercept administered at either (i) a 4-week interval or (ii) an 8-week dosing interval, ***including one additional dose at week 4***—i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. (Ex.1007, Adis, 263; Ex.1002, Albini ¶¶ 85-86) (color-coded in accord with modified Figure 1 above)). As support for these disclosures, Adis cites four Regeneron and Bayer press releases issued in 2007 and 2008. (Ex.1007, Adis, 263, 268 (Ref. Nos. 10-14); Ex.1002, Albini ¶¶ 86, 89).

Adis further discloses Regeneron's Phase 2 trial evaluating a four monthly dose regimen that resulted in a statistically significant reduction in retinal thickness

(a primary indicator used in AMD treatment). (Ex.1007, Adis, 263; Ex.1002, Albini ¶¶ 87-88).

3. Regeneron (8-May-2008) (Ex.1013).

Regeneron (8-May-2008) published on May 8, 2008, and thus constitutes prior art under 35 U.S.C. § 102.[9] To Petitioner's knowledge, Regeneron (8-May-2008)—or any other relevant Regeneron/Bayer press release—was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (*See* Ex.1001, '338 patent, References Cited).

Regeneron (8-May-2008) reports VIEW1/VIEW2 Phase 3 AMD trials and sets forth the dosing regimen encompassed by the Challenged Claims: "In the first year, the VIEW2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at . . . 2.0 mg at an 8-week dosing interval, ***including one additional 2.0 mg dose at week four*** [i.e., doses at weeks **0, 4, 8, 16, 24, 32, 40, and 48**]." (Ex.1013, Regeneron (8-May-2008), 1 (emphasis added); Ex.1002, Albini ¶ 91).

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[9] Regeneron (8-May-2008) was publicly available to skilled artisans long before January 13, 2011, as was the corresponding Bayer press release (Ex.1032). (Ex.1007, Adis, 268 (Ref. No. 13) (citing Bayer (8-May-2008)); Ex.1003, Gerritsen ¶¶50-56; Ex.1002, Albini ¶90)).

Regeneron (8-May-2008) also reports that "[r]esults from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision." (Ex.1013, Regeneron (8-May-2008), 1; Ex.1002, Albini ¶ 92).

4. NCT-795 (Ex.1014).

NCT-795 is an on-line record disclosing the VIEW1 regimen Regeneron submitted to the ClinicalTrials.gov database maintained by the National Library of Medicine at the National Institutes of Health ("NIH"). ClinicalTrials.gov is a website "***intended for a wide audience***, including individuals with serious or life-threatening diseases or conditions, members of the public, ***health care providers, and researchers***." (*See* Ex.1086, History-ClinicalTrials.gov, 2 (emphasis added)). After Congress passed the Food and Drug Modernization Act of 1997, which required "a public information resource on certain clinical trials," NIH created ClinicalTrials.gov in 2000. (*Id.*). In 2007, Congress expanded the requirements for submitting clinical trial information with laws penalizing non-compliance, including "withholding of NIH grant funding and civil monetary penalties of up to $10,000 a day." (*Id.*).

As shown in the following, NCT-795 is a § 102 printed publication. *See Hulu, LLC v. Sound View Innovations*, No. IPR2018-01039, 2019 WL 7000067, *5 (P.T.A.B. Dec. 20, 2019) ("[A]t the institution stage, the petition must identify, with

particularity, evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication.").

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

Here, the evidence confirms that NCT-795—including the VIEW1 dosing regimen and other clinical study details provided therein—was publicly available on the ClinicalTrials.gov website prior to January 13, 2011. ***First***, the History of Changes archive that ClinicalTrials.gov maintains for each study demonstrates the VIEW1 regimen was disclosed to the public before 2011. (Ex.1014, NCT-795, 8). ***Second***, Wayback Machine records and the corresponding affidavit provided herein (Ex.1087, Wayback-Affidavit-338, 1-2, 8-11) show NCT-795's public availability prior to 2011. *Sandoz Inc. v. Abbvie Biotechnology Ltd.*, No. IPR2018-00156, 2018 WL 2735468, *4-5 (P.T.A.B. June 5, 2018) (finding Wayback Machine screenshot and expert testimony adequate evidence to establish FDA website as a prior art printed publication). ***Third***, NCT-795 was expressly cited in the prior art itself (*see,*

e.g., Ex.1006, Dixon, 1579 (Bibliography No. 46) ("Accessed 28 Sep 2008"); Ex.1072, Reichert, 94-95), demonstrating its actual publication and availability to interested, skilled artisans in at least September 2008. (Ex.1003, Gerritsen ¶¶ 82-87; Ex.1002, Albini ¶ 82).

Finally, in support of this Petition, Dr. Gerritsen declares in her experience and expert opinion that clinical study details were publicly accessible from ClinicalTrials.gov to skilled artisans—who were both interested in and familiar with such reports—as of their posted dates. (Ex.1003, Gerritsen ¶¶ 76-77; *see also* Albini ¶¶ 93-99). As such, NCT-795 is a printed publication that was accessible to the relevant public more than one year before January 13, 2011 and thus constitutes prior art under 35 U.S.C. § 102. In addition, to Petitioner's knowledge, NCT-795 was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, '338 patent, References Cited).

NCT-795 discloses Regeneron's Phase 3 VIEW1 trial. (Ex.1014, NCT-795, 3-5). Specifically, NCT-795 discloses the treatment arms of the VIEW1 study, including the every-8-week treatment regimen: "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (Ex.1014, NCT-795, 4-5, 8; Ex.1002, Albini ¶¶ 100-03) (i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, 48**, etc.).

5. NCT-377 (Ex.1015).

NCT-377, like NCT-795 (above), is an on-line record from NIH's ClinicalTrials.gov website describing the VIEW2 Study. As shown, NCT-377 is also a § 102 printed publication. *Hulu*, 2019 WL 7000067, *5; *see also Grünenthal*, 2020 WL 4341822, at *8 (determining that a printout from ClinicalTrials.gov qualified as a prior art printed publication).

Each of the following independently confirm that NCT-377 (including the study details and dosing regimen provided therein) was publicly available and accessible to interested, skilled artisans prior to Jan. 13, 2011 (*see* MPEP § 2128): (i) the History of Changes archive for NCT-377 (Ex.1015, NCT-377, 1-3); (ii) Wayback Machine records and the corresponding affidavit provided herein (Ex.1087, Wayback-Affidavit-338, 1-2, 4-7, 11; *see Sandoz*, 2018 WL 2735468, at *4-5); (iii) prior art references expressly citing NCT-377 (Ex.1006, Dixon, 1579 (Bibliography No. 47) ("Accessed 28 Sep 2008"); Ex.1072, Reichert, 95-96); and (iv) Dr. Gerritsen's declaration, providing her experience and expert opinion. (Ex.1003, Gerritsen ¶¶ 76-77, 79-85, 87-89; *see also* Albini ¶¶ 82, 104-06).

As such, NCT-377 thus constitutes prior art under 35 U.S.C. § 102. In addition, to Petitioner's knowledge, NCT-377 was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (*See* Ex.1001, '338 patent, References Cited).

NCT-377 describes Regeneron's VIEW2 trial: "a phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration." (Ex.1015, NCT-377, 5). NCT-377 discloses the treatment arms for the VIEW2 trial, including the every-8-week dosing regimen: "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year [i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**]." (Ex.1015, NCT-377, 5-6 (emphasis added); Ex.1002, Albini ¶¶ 106-09).

6. The '758 patent (Ex.1010).

The '758 patent issued on May 20, 2008, and thus constitutes prior art under 35 U.S.C. § 102. To Petitioner's knowledge, the '758 Patent was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, '338 patent, References Cited).

The '758 patent discloses "[m]odified chimeric polypeptides with improved pharmacokinetics," including, *inter alia*, the VEGF $Trap_{R1R2}$ (i.e., VEGF Trap-Eye/aflibercept) fusion protein. (Ex.1010, '758 patent, Abstract; *id.*, 19:15-17; *id.*, 29:39-56). The aflibercept sequence is disclosed in Figures 24A-C. (*Compare* Ex.1001, '338 patent, SEQ ID NO:1 and SEQ ID NO:2, *with* Ex.1010, '758 patent, Fig.24A-C; *see also* Ex.1024, '758 FH, 12/22/2011 PTE, 2, 6-7; Ex.1002, Albini ¶¶ 44, 114-15; Ex.1093; Ex.1094).

The ’758 patent also teaches that aflibercept may be useful for treating eye disorders such as AMD. (Ex.1010, ’758 patent, 15:50-16:6; *see also id.*, 3:5-29; Ex.1002, Albini ¶¶ 114-15).

7. Dix (Ex.1033).

Dix published in 2006, and thus constitutes prior art under 35 U.S.C. § 102. The Examiner did not consider Dix. (Ex.1001, ’338 patent, References Cited).

Dix teaches pharmaceutical formulations comprising agents capable of inhibiting VEGF; the VEGF Trap fusion protein (aflibercept) disclosed in Holash is Dix’s “preferred” VEGF antagonist. (Ex.1033, Dix, Abstract; *id.*, [0005], [0014], [0030]).

The VEGF Trap sequences disclosed in Dix are the same sequences for aflibercept required under the Challenged Claims. (*Compare* Ex.1001, ’338 patent, SEQ ID NO:1 and SEQ ID NO:2, *with* Ex.1033, Dix, 9-11 (SEQ ID NO:3 & SEQ ID NO:4); Ex.1002, Albini ¶¶ 116-18; Ex.1093; Ex.1094).

XI. GROUNDS FOR UNPATENTABILITY—DETAILED ANALYSIS.

A. ANTICIPATION.

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

1. Legal standards.

Anticipation requires that a “single prior art reference disclose[], either

expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002).

An inherent disclosure requires that "the natural result flowing from the operation as taught would result in the performance of the questioned function." *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275 (Fed. Cir. 2010). Newly discovered results or new benefits of a known process directed to the same purpose are not patentable because such results are inherent. *Id.*; *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007); *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005) (preamble reciting "method for treating skin sunburn" was inherently anticipated where the court found that "[i]f [the prior art reference] discloses the very same methods, then the particular benefits must naturally flow from those methods even if not recognized as benefits at the time of [the prior art's] disclosure").

In addition, "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers*, 246 F.3d 1379. Here, the Challenged Claims require only a dosing regimen without any particular efficacy or result (Ex.1002, Albini ¶¶ 43, 128), and therefore, "proof of efficacy is not required in order for a [prior art] reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

2. Ground 1: Dixon anticipates the Challenged Claims.

Independent Claims 1 and 14 are anticipated by Dixon, which, as shown in the following tables, and confirmed by Dr. Albini (Ex.1002, ¶¶ 119-28, 147-50), discloses each and every element:

Claim 1:	**Dixon:**
A method for treating an angiogenic eye disorder in a patient,	"VEGF Trap-Eye is a novel anti-VEGF therapy, with Phase I and Phase II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Ex.1006, Dixon, 1573, 1577). Phase 2 patients "treated with 2.0 mg or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p<0.0001$) and 5.4 ($p<0.085$) ETDRS letters with 29 and 19% gaining, respectively, ≥ 15 ETDRS letters at 52 weeks." (*Id*., 1576). "[P]atients . . . demonstrated stabilization of their vision that was similar to previous studies of ranibizumab at 1 year." (*Id.*, 1577). "Two Phase III studies in wet AMD [VIEW1/VIEW2] are currently under way and seek to compare monthly ranibizumab to monthly or bimonthly VEGF Trap-Eye." (*Id.*, 1577-78 (describing DME and RVO studies)). (Ex.1002, Albini ¶ 128).

Claim 1:	**Dixon:**
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	"[Phase 3] will evaluate the safety and efficacy of . . . 2.0 mg at an 8 week dosing interval (***following three monthly doses***)." (Ex.1006, Dixon, 1576 (emphasis added)). In other words, an "initial dose" at day 0, "secondary doses" at weeks 4 and 8; and "tertiary doses" of every 8 weeks beginning at week 16 (i.e., doses at week **0, 4, 8, 16, 24, 32, 40, and 48**). (Ex.1002, Albini ¶¶ 119-28).
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(*Id.*).
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	(*Id.*).
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2.	VEGF Trap-Eye is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG." (Ex.1006, Dixon, 1576 (Fig.1)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575). (Ex.1002, Albini ¶ 127).

The amino acid sequence and structural information for VEGF Trap-Eye recited in the third "wherein" clause was well-known and widely-published to

skilled artisans. (*See, e.g.*, Ex.1010, '758 patent, Fig.24A-C, 10:15-17; Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1002, Albini ¶¶ 147-50). Dixon's express disclosure of VEGF Trap-Eye thus anticipates. *In re Baxter Travenol Labs*, 952 F.2d 388, 390 (Fed. Cir. 1991) ("extrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference")

The analysis for **Claim 14** is nearly identical. First, the dosing regimen elements are the same, which Dixon anticipates for the reasons stated above. Second, claim 14 uses the nucleotide sequence, as opposed to the amino acid sequence used in claim 1 to identify VEGF Trap-Eye—substantively identical limitations.

Like the amino acid sequence, the nucleotide sequence for VEGF Trap-Eye was disclosed in the prior art and well known to skilled artisans. (Ex.1002, Albini ¶¶ 147-50). Accordingly, Dixon's disclosure anticipates the third "wherein" clause of claim 14 as well:

Claim 14:	**Dixon:**
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.	VEGF Trap-Eye is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached to the Fc fragment of human IgG." (Ex.1006, Dixon, 1576 (Fig.1)).

	"VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575).[10] (Ex.1002, Albini ¶¶ 147-50).

Claims 3 and 16 further limit the claimed dosing regimen as follows: "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose"—i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. Dixon expressly discloses this exact regimen, i.e., an initial dose at day 0 and two secondary doses at weeks 4 and 8. (Ex.1006, Dixon, 1576 ("three monthly doses"), Ex.1002, Albini ¶¶ 129-32, 151-53; *see also* Fig.1 (*supra* § X(B)(1) (**blue arrows**))). Accordingly, Dixon anticipates.

Claims 4 and 17 further limit the claimed method as follows: "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose." As stated above, Dixon expressly discloses doses of "2.0 mg at an 8 week dosing interval," (Ex.1006, Dixon, 1576), which anticipates the added limitation. (Ex.1002, Albini ¶¶ 129-32, 151-53; *see also* Fig. 1 (*supra* § X(B)(1) (**red arrows**))).

[10] *See supra* n.11.

Claims 5 and 19 further limit the claimed method as follows: "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose." The VIEW1 study continued for at least one year, (Ex.1006, Dixon, 1576 ("[a]fter the first year of the study")), which, under the proposed regimen, would yield "at least 5 tertiary doses" administered eight weeks apart. (Ex.1002, Albini ¶¶ 133-35, 157-60; *see also* Fig.1 (*supra* § X(B)(1) (**red arrows**))). Accordingly, Dixon discloses the added limitation, and thus, anticipates.

Claims 6, 7, 18, and 20 further limit the "angiogenic eye disorder" to, *inter alia*, AMD. Dixon discloses administering VEGF Trap-Eye to patients with AMD. (Ex.1006, Dixon, 1573; *id*., 4 (the Phase 3 trial "will enroll ~1200 patients with neovascular AMD"); Ex.1002, Albini ¶¶ 136-38, 154-56). Accordingly, Dixon discloses the added limitation, and thus anticipates.

Claims 8-10 and 21-23 further limit the claimed method to, *inter alia*, "intraocular administration" or, more specifically "intravitreal administration" (Claims 10 and 23). Intravitreal administration is a subset of intraocular administration and refers to administration directly into the vitreous of the eye. (Ex.1002, Albini ¶¶ 139-43, 161-66; Ex.1001, '338 patent, 2:38-41 ("Various

administration routes are contemplated . . . including . . . intraocular administration (e.g., intravitreal administration).")). Dixon disclosed that VIEW will evaluate "the safety and efficacy of intravitreal VEGF Trap-Eye." (Ex.1006, Dixon, 1576). Accordingly, Dixon discloses the additional limitations, and thus anticipates.

Claims 11, 13, 24, and 26 further limit the claimed method to, *inter alia*, doses of "about 2 mg of the VEGF antagonist." Dixon discloses 0.5 and 2.0 mg VEGF Trap-Eye doses. (Ex.1006, Dixon, 1576; Ex.1002, Albini ¶¶ 144-46, 167-69). Dixon explains that the 2 mg intravitreal dose "allows for extended blocking of VEGF in the eye, but would be predicted to give negligible systemic activity as it will be rapidly bound to VEGF and inactivated." (*Id.*, 1575). Dixon discloses that the VIEW regimens "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye [2 mg] . . . at an 8 week dosing interval (following three monthly doses)." (*Id.*, 1576). Accordingly, Dixon discloses the additional limitations, and thus, anticipates.

3. Ground 2: Adis anticipates the Challenged Claims.

Adis describes Phase 1, 2, and 3 clinical trials studying VEGF Trap-Eye as a therapy for treating angiogenic eye disorders such as AMD—anticipating the Challenged Claims.

Independent Claims 1 and 14 are anticipated by Adis, which, as shown in the following tables, and confirmed by Dr. Albini (Ex.1002, Albini ¶¶ 170-77, 197-

200), discloses each and every element:

Claim 1:	**Adis:**
A method for treating an angiogenic eye disorder in a patient,	"Regeneron and Bayer are developing [aflibercept] for eye disorders." (Ex.1007, Adis, 261; *id.*, 263). "Blockade of VEGF can also prevent blood vessel formation and vas[cu]lar leakage associated with wet [AMD]." (*Id.*). "A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008." (*Id.*). "Regeneron has completed a 12-week, phase II trial in patients with wet AMD, to evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens . . . . Analysis of data demonstrated that all five doses of aflibercept met the primary endpoint of a statistically significant reduction in retinal thickness after 12 weeks and 32 weeks of treatment compared with baseline." (*Id.*; *see also id.*, 267-68). (Ex.1002, Albini ¶ 172).
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	"The non-inferiority, [VIEW1] . . . study will evaluate the safety and efficacy of intravitreal aflibercept at . . . *2.0 mg at an 8-week dosing interval* . . . ." (Ex.1007, Adis, 263 (emphasis added)).

Claim 1:	**Adis:**
	"[VIEW 2] will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at . . . *2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4*." (*Id.* (emphasis added)). In other words, an "initial dose" at day 0, "secondary doses" at weeks 4 and 8; and "tertiary doses" every 8 weeks beginning at week 16 (i.e., weeks **0, 4, 8**, **16, 24, 32, 40, and 48**). (Ex.1002, Albini ¶¶ 172-75).
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(Ex.1007, Adis, 263).
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	(*Id.*).
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2.	"Aflibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the Fc region of human IgG." (Ex.1007, Adis, 261). (Ex.1002, Albini ¶ 176).

The analysis for **Claim 14**, as explained above, is nearly identical to claim 1 because (i) the dosing regimen elements are the same and (ii) the third "wherein"

clauses for each—i.e., the VEGF Trap-Eye limitations—are substantively identical. Both the amino acid and nucleotide sequences for VEGF Trap-Eye were published in the prior art and known to skilled artisans. (Ex.1002, Albini ¶¶ 197-200). Adis discloses the "VEGF antagonist" of claim 14, and thus anticipates:

Claim 14:	**Adis:**
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.	"Aflibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the Fc region of human IgG." (Ex.1007, Adis, 261).[11] (Ex.1002, Albini ¶ 199).

Claims 3 and 16 further limit the claimed dosing regimen to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose"—i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. Adis discloses "an 8-week dosing interval, including one additional 2.0 mg dose at week 4" (Ex.1007, Adis, 263), i.e., a single initial dose (week 0) plus two secondary doses administered at weeks 4 and 8, (Ex.1002, Albini ¶¶ 178-81, 201-03; *see also* Fig.1 (*supra* § X(B)(1) (**blue**

[11] Adis confirms VEGF Trap-Eye and aflibercept are the same molecule. (Ex.1007, Adis, 261; Ex.1002, Albini ¶176).

arrows))). Accordingly, Adis discloses the added limitations and thus anticipates.

Claims 4 and 17 further limit the claimed method to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose." Adis expressly discloses "2.0 mg at an 8-week dosing interval." (Ex.1007, Adis, 263; Albini ¶¶ 178-81, 201-03). Accordingly, Adis discloses the added limitation, and thus anticipates.

Claims 5 and 19 further limit the claimed method to: "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose." The VIEW1/VIEW2 Phase 3 trials continued for at least one year (*see* Ex.1007, Adis, 263 ("Patients will continue to be treated and followed for an additional year, after the first year of treatment.")), which, under the proposed regimen, would yield "at least 5 tertiary doses" administered eight weeks apart (Ex.1002, Albini ¶¶ 182-85, 207-09). Accordingly, Adis discloses the added limitations, and thus anticipates.

Claims 6, 7, 18, and 20 further limit the "angiogenic eye disorder" to, *inter alia*, AMD. Adis discloses administering aflibercept for eye disorders, including AMD. (Ex.1007, Adis, 261, 263-64 (Phase 2 and 3 trials in wet AMD patients); *id.*, 265-66 (Table II), 267-68; Ex.1002, Albini ¶¶ 186-88, 204-06). Accordingly, Adis

discloses the additional limitations, and thus anticipates.

Claims 8-10 and 21-23 further limit the claimed method to, *inter alia*, "intraocular administration" or, more specifically "intravitreal administration" (Claims 10 and 23). Adis discloses these elements. (Ex.1007, Adis, 263; *see also id.*, 263-264 ("intravitreal injection as a route of administration"); *id.*, 265-66 (Table II); *id.*, 268 (Phase 1 trials in AMD with intravitreal aflibercept); Ex.1002, Albini ¶¶ 189-93, 210-14). Accordingly, Adis anticipates.

Claims 11, 13, 24, and 26 further limit the claimed method to, *inter alia*, doses of "about 2 mg of the VEGF antagonist." Adis discloses Phase 3 AMD trials "of intravitreal aflibercept at doses of . . . 2.0 mg." (Ex.1007, Adis, 263; Ex.1002, Albini ¶¶ 194-96, 215-17). Accordingly, Adis discloses the additional limitations, and thus anticipates.

4. Ground 3: Regeneron (8-May-2008) anticipates the Challenged Claims.

Regeneron (8-May-2008) describes Phase 2 and 3 trials of VEGF Trap-Eye in AMD using the claimed dosing regimens—thereby disclosing all limitations and thus anticipating the Challenged Claims.

Independent Claims 1 and 14 are anticipated by Regeneron (8-May-2008), which, as shown in the following tables, and confirmed by Dr. Albini (Ex.1002, ¶¶ 218-22, 243-46), discloses each and every element:

Claim 1:	**Regeneron (8-May-2008):**
A method for treating an angiogenic eye disorder in a patient,	"Results from the Phase 2 study have shown that VEGF Trap-Eye has the potential to significantly reduce retinal thickness and improve vision." (Ex.1013, Regeneron (8-May-2008), 1). "VEGF Trap-Eye met both primary and secondary key endpoints: a statistically significant reduction in retinal thickness (a measure of disease activity) after 12 weeks of treatment compared with baseline and a statistically significant improvement from baseline in visual acuity (ability to read letters on an eye chart)." (*Id.*, 1-2). "Dosing of the first patient in this confirmatory Phase 3 trial is an important milestone for this compound intended to treat a devastating ocular disease that impacts millions of people worldwide." (*Id.*, 1). (Ex.1002, Albini ¶ 219; *see also id.*, ¶ 128).
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	The Phase 3 VIEW2 "study will evaluate the safety and efficacy of VEGF Trap-Eye at . . . *2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four*." (Ex.1013, Regeneron (8-May-2008), 1 (emphasis added)). In other words, doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**.

Claim 1:	**Regeneron (8-May-2008):**
	(Ex.1002, Albini ¶¶ 219-20).
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(*Id*.).
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	(*Id*.).
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2.	"VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A . . . and VEGF-B. VEGF Trap-Eye is a specific and highly potent blocker of these growth factors." (Ex.1013, Regeneron (8-May-2008), 2). (Ex.1002, Albini ¶ 221).

The analysis for **Claim 14**, as explained above, is nearly identical to claim 1 because (i) the dosing regimen elements are the same and (ii) the third "wherein" clauses for each—i.e., the VEGF Trap-Eye limitations—are substantively identical. Both the amino acid and nucleotide sequences for VEGF Trap-Eye (i.e., aflibercept) were published in the prior art and known to skilled artisans. (Ex.1002, Albini ¶¶ 243-46). Regeneron (8-May-2008) discloses the "VEGF antagonist" of claim 14, and thus anticipates:

Claim 14:	**Regeneron (8-May-2008):**
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.	"VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A . . . and VEGF-B. VEGF Trap-Eye is a specific and highly potent blocker of these growth factors." (Ex.1013, Regeneron (8-May-2008), 2). (Ex.1002, Albini ¶ 245).

Claims 3 and 16 further limit the claimed dosing regimen as follows: "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose"—i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. Regeneron (8-May-2008) expressly discloses "8-week dosing interval, including one additional 2.0 mg dose at week four"—i.e., a single initial dose (week 0) plus two secondary doses administered four weeks apart (weeks 4 and 8). (Ex.1013, Regeneron (8-May-2008), 1; Ex.1002, Albini ¶¶ 223-26, 247-50). Accordingly, Regeneron (8-May-2008) discloses the added limitations, and thus anticipates.

Claims 4 and 17 further limit the claimed method as follows: "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose." Regeneron (8-May-2008) discloses "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, Regeneron (8-May-2008), 1;

Ex.1002, Albini ¶¶ 223-226, 247-250). Accordingly, Regeneron (8-May-2008) discloses the added limitation, and thus anticipates.

Claims 5 and 19 further limit the claimed method as follows: "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose." The Phase 3 AMD study continued for at least one year (Ex.1013, Regeneron (8-May-2008), 1 ("In the first year . . .")), which, under the proposed regimen, would yield "at least 5 tertiary doses" administered eight weeks apart. (Ex.1002, Albini ¶¶ 227-29, 255-57). Accordingly, Regeneron (8-May-2008) discloses the added limitations, and thus anticipates.

Claims 6, 7, 18, and 20 further limit the "angiogenic eye disorder" to, *inter alia*, AMD. Regeneron (8-May-2008) discloses, *inter alia*, Phase 3 trials directed to AMD patients. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1002, Albini ¶¶ 230-33, 251-54). Accordingly, Regeneron (8-May-2008) discloses the additional limitation, and thus anticipates.

Claims 8-10 and 21-23 further limit the claimed method to, *inter alia*, "intraocular administration" or, more specifically "intravitreal administration" (Claims 10 and 23). (Ex.1002, Albini ¶¶ 234-38, 258-62; *see also* Ex.1001, '338 patent, 2:38-41, 23:48-49 (Claim 10)). Regeneron (8-May-2008) discloses

intravitreal injection. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1002, Albini ¶¶ 234-38, 258-62). Accordingly, Regeneron (8-May-2008) discloses the additional limitation, and thus anticipates.

Claims 11, 13, 24, and 26 further limit the claimed method to, *inter alia*, doses of "about 2 mg of the VEGF antagonist." Regeneron (8-May-2008) discloses 2.0 mg doses to treat AMD. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1002, Albini ¶¶ 239-42, 263-66). Accordingly, Regeneron (8-May-2008) discloses the additional limitation, and thus anticipates.

5. Grounds 4 and 5: NCT-795 and NCT-377 each anticipate the Challenged Claims.

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

Independent Claims 1 and 14 are anticipated by NCT-795 and NCT-377, which, as shown in the following tables, and confirmed by Dr. Albini (Ex.1002, ¶¶ 267-70, 291-94, 315-19, 340-43), disclose each and every element:

Claim 1:	**NCT-795:**	**NCT-377:**
A method for treating an angiogenic eye disorder in a patient,	"A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap	"A Randomized, Double Masked, Active Controlled Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap

Claim 1:	**NCT-795:**	**NCT-377:**
	in Subjects With [AMD]." (Ex.1014, NCT-795, 3; *id.*, 4).	in Subjects With [AMD]." (Ex.1015, NCT-377, 3).
	(Ex.1002, Albini ¶¶ 267-68, 315-16; *see also id.*, ¶ 128).	
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	"2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (Ex.1014, NCT-795, 8).	"2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6).
	In other words, an "initial dose" at day 0, "secondary doses" at weeks 4 and 8; and "tertiary doses" every 8 weeks beginning at week 16 (i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**). (Ex.1002, Albini ¶¶ 268, 316).	
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	(*Id.*).	(*Id.*).
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	(*Id.*).	(*Id.*).
wherein the VEGF antagonist is a VEGF receptor-based chimeric	"[S]tudy of the efficacy and safety of VEGF Trap-Eye in patients with	"[S]tudy of the efficacy and safety of VEGF Trap-Eye in patients with

<table>
<tr><th><u>Claim 1</u>:</th><th><u>NCT-795</u>:</th><th><u>NCT-377</u>:</th></tr>
<tr><td rowspan="2">molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2.</td><td>neovascular age-related macular degeneration.” (Ex.1014, NCT-795, 4).</td><td>neovascular age-related macular degeneration.” (Ex.1015, NCT-377, 5).</td></tr>
<tr><td colspan="2">(Ex.1002, Albini ¶¶ 269, 318).</td></tr>
</table>

The analysis for **Claim 14**, as explained above, is nearly identical to claim 1 because (i) the dosing regimen elements are the same and (ii) the third “wherein” clauses for each—i.e., the VEGF Trap-Eye limitations—are substantively identical. Both the amino acid and nucleotide sequences for VEGF Trap-Eye (i.e., aflibercept) were published in the prior art and known to skilled artisans. (Ex.1002, Albini ¶¶ 291-94, 340-43). NCT-795, and NCT-377 disclose the “VEGF antagonist” of claim 14, and thus anticipate:

Claim 14:	**NCT-795:**	**NCT-377:**
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.	"[S]tudy of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration." (Ex.1014, NCT-795, 4; Ex.1015, NCT-377, 5 (same)). (Ex.1002, Albini ¶¶ 291-94, 340-43).	

Claims 3 and 16 further limit the claimed dosing regimen as follows: "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose"—i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**. NCT-795 and NCT-377 disclose "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year," (Ex.1014, NCT-795, 8; Ex.1015, NCT-377, 6), i.e., a single initial dose plus two secondary doses administered four weeks apart. (Ex.1002, Albini ¶¶ 271-74, 295-98, 320-23, 344-47). Accordingly, NCT-795 and NCT-377 respectively disclose the additional limitations, and thus each anticipates.

Claims 4 and 17 further limit the claimed method as follows: "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose." NCT-795 and NCT-377 respectively disclose "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first

year." (Ex.1014, NCT-795, 8; Ex.1015, NCT-377, 6; Ex.1002, Albini ¶¶ 271-74, 295-98, 320-23, 344-47). As such, NCT-795, and NCT-377 respectively disclose the additional limitation, and thus each anticipates.

Claims 5 and 19 further limit the claimed method as follows: "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose." The Phase 3 studies continued for at least one year, (Ex.1014, NCT-795, 8); Ex.1015, NCT-377, 6), which, under the proposed regimen, would yield "at least 5 tertiary doses" administered eight weeks apart (Ex.1002, Albini ¶¶ 275-77, 303-05, 324-26, 352-54). As such, NCT-795 and NCT-377 respectively disclose the additional limitations, and thus each anticipates.

Claims 6, 7, 18, and 20 further limit the "angiogenic eye disorder" to, *inter alia*, AMD. NCT-795 and NCT-377 disclose Phase 3 trials directed to AMD patients. (Ex.1014, NCT-795, 4; Ex.1015, NCT-377, 5; Ex.1002, Albini ¶¶ 278-81, 299-302, 327-30, 348-51). Accordingly, NCT-795 and NCT-377 disclose the additional limitations, and thus each anticipates.

Claims 8-10 and 21-23 further limit the claimed method to, inter alia, "intraocular administration" or, more specifically "intravitreal administration" (Claims 10 and 23). NCT-795 and NCT-377 disclose intravitreal administration.

(Ex.1014, NCT-795, 3; Ex.1015, NCT-377, 4; Ex.1002, Albini ¶¶ 282-86, 306-10, 331-35, 355-59). Accordingly, NCT-795 and NCT-377 respectively disclose the additional limitations, and thus each anticipates.

Claims 11, 13, 24, and 26 further limit the claimed method to, *inter alia*, doses of "about 2 mg of the VEGF antagonist." NCT-795 and NCT-377 disclose patients receiving 2.0 mg doses of VEGF Trap-Eye at the claimed dosing regimen. (Ex.1014, NCT-795, 8; Ex.1015, NCT-377, 6). Accordingly, NCT-795 and NCT-377 respectively disclose the additional limitations, and thus each anticipates. (Ex.1002, Albini ¶¶ 287-90, 311-14, 336-39, 360-63).

* * *

Each anticipatory reference asserted herein (Dixon, Adis, Regeneron (8-May-2008), NCT-795, NCT-377) is presumed enabling and it is Regeneron's burden to rebut those presumptions. *See, e.g.*, *In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012); *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 659-60 (D. Del. 2014) (rejecting patentee's arguments that prior art reference was not enabled where reference disclosed exact dosage amount and dosing interval in claims, and thus also inherently disclosed the claimed "minimizing skeletal muscle toxicity"). Any attempted rebuttal here would be futile because each reference sets forth a clear method and dosing regimen that a skilled artisan would have no trouble following. Moreover, the Challenged Claims' preamble—even if it is assumed

limiting (it is not)—does not help Regeneron. Petitioner's references disclose Phase 2 data of "treating" AMD with VEGF Trap-Eye; treating which was accomplished using even fewer doses, on average, than the Phase 3 every-8-week VIEW regimen, confirming that the above references' disclosures of the VIEW every-8-week dosing were enabling. (Ex.1006, Dixon, 1576; Ex.1007, Adis, 267-68; Ex.1013, Regeneron (8-May-2008), 1-2; Ex.1056, Regeneron (28-September-2008), 1-2). Further, "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers*, 246 F.3d at 1376. In addition to the Phase 2 data, this inherency is illustrated by the Phase 3 results using the prior art Phase 3 dosing method set forth in each of the above anticipatory references well before the filing date of the '338 patent. (Ex.1018, Heier-2012, 2541-45). The Phase 3 results reported that "[i]ntravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab." (*Id.*, 2357). From these results the authors concluded that "aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections." (*Id*.).

The same analysis applies to Regeneron's potential proposed construction of "tertiary dose," to the extent that Regeneron attempts to propose that construction in this IPR. As Petitioner states above, Regeneron's proposed construction ignores the

express definition provided in the specification and should be rejected. However, to the extent it is adopted by the Board, the Phase 2 data already had shown that extended dosing regimens of VEGF Trap-Eye were capable of maintaining a therapeutic benefit throughout the course of treatment, and did so with even fewer doses, on average, than the every-8-week VIEW regimen. This Phase 2 data was widely reported and available to skilled artisans well before the filing date of the '338 patent. (Ex.1006, Dixon, 1576; Ex.1007, Adis, 267-68; Ex.1013, Regeneron (8-May-2008), 1-2; Ex.1056, Regeneron (28-September-2008), 1-2).

B. Obviousness.

Even if not anticipated (and they surely are), the Challenged Claims would have been obvious over Dixon alone or in view of various combinations of the prior art, including the '758 patent and/or Dix, as explained in the following:

1. Legal standard.

A patent claim is invalid under 35 U.S.C. § 103(a) if 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 a person having ordinary skill in the pertinent art. *KSR*, 550 U.S. at 406. Furthermore, "[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." *Id.* at 421.

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

2. Ground 6: The Challenged Claims are obvious over Dixon[12] (either alone or in combination with the '758 patent or Dix).

As discussed above, Dixon discloses each and every element of the Challenged Claims and thus anticipates them. Notwithstanding, Dixon also renders the Challenged Claims obvious in light of the skilled artisan's (i) knowledge of the

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[12] As described in more detail above (*supra* § XI(A)), several prior art references asserted herein (i.e., Adis, Regeneron (8-May-2008), NCT-795, and NCT-377) disclose the same VIEW1/VIEW2 dosing regimen as Dixon. Accordingly, the Challenged Claims are equally obvious over each of those references (either alone or in combination with the '758 patent and/or Dix).

sequence and molecular structure for VEGF Trap-Eye; (ii) clear motivation—as expressly stated in Dixon—to explore less frequent dosing; and (iii) reasonable expectation of success found in Dixon's disclosure of the positive Phase 2 trial data for VEGF Trap-Eye. (Ex.1002, Albini ¶¶ 364-403).

First, numerous Regeneron publications and patent submissions disclosed the VEGF Trap-Eye sequence and domain architecture. (*See, e.g.*, Ex.1010, '758 patent, Fig.24A-C; *id.*, 15:50-16:6; Ex.1033, Dix, [0005], [0013]-[0014], [0030]) (including the embodiment without the signal sequence or the C-terminal lysine); Ex.1002, Albini, ¶¶ 369, 390). As such, a skilled artisan would have understood Dixon's disclosure of VEGF Trap-Eye/aflibercept to refer to those prior art sequences/structures. Dixon alone is sufficient, but in any event, the '758 patent and Dix each also set forth the precise structure and sequence for VEGF Trap-Eye/aflibercept.

Second, prior to the earliest priority date of the Challenged Claims (January 13, 2011), a known problem in treating angiogenic eye disorders existed in the art for which the prior art expressly disclosed an obvious solution. *See KSR*, 550 U.S. at 419-20. Specifically, as Dixon identifies, frequent intraocular injections (as often as monthly) presented a "significant" drawback to the then-existing AMD therapy. (Ex.1006, Dixon, 1577 ("significant time and financial burden falls on patients during their [monthly] treatment course" and "[d]esirable attributes for emerging

therapies for neovascular AMD include . . . decreased dosing intervals"); Ex.1002, Albini ¶ 365). In response to the known "time and financial burden[s] of monthly injections," Dixon discusses "the initiation of studies to examine the efficacy of ***alternative dosing schedules***." (*Id.*, 1574 (emphasis added)). Dixon, in fact, directly recommends using a dosing regimen featuring longer intervals to minimize the treatment burden, which would have motivated a skilled artisan to adopt the disclosed Phase 3 regimen—an obvious solution to the need for less frequent injections. (Ex.1002, Albini ¶ 366). In other words, Dixon "go[es] beyond just illuminating a known problem; [it] also expressly propose[s] the claimed solution." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1375-76 (Fed. Cir. 2013).

Third, a skilled artisan would reasonably expect success administering the VIEW1/VIEW2 dosing regimens to AMD patients. As Dixon reports, the Phase 2 CLEAR-IT-2 AMD trials were so promising that Phase 3 trials involving >2000 patients were launched—in other words, skilled artisans expected success. Yet, § 103 "does not require absolute predictability of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Rather, a skilled artisan must merely have a *reasonable* expectation that it would work for its intended purpose for a claimed invention to be obvious under § 103. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Indeed, prior art creates a reasonable expectation of success

where it "guide[s]," or "funnels" the skilled artisan to a particular approach. *Bayer Schering Pharma AG v. Barr Lab'ys, Inc.*, 575 F.3d 1341, 1347, 1350 (Fed. Cir. 2009). Here, Dixon does that and more. Dixon reports increases in visual acuity and mean decreases in retinal thickness resulting from the Phase 2 regimen (four monthly loading doses followed by PRN dosing). (Ex.1006, Dixon, 1576; Ex.1002, Albini ¶¶ 367-68). Moreover, Dixon reports that Phase 2 patients required (on average) *only 1.6 additional injections* after the four monthly loading doses during the year-long study—further confirming the skilled artisan's expectation of success with the VIEW1/VIEW2 dosing regimen, which would deliver *more* frequent injections than the average given during the Phase 2 trial.[13] (Ex.1002, Albini ¶¶ 367-68).

In sum, Dixon alone renders the Challenged Claims obvious based on the same disclosures applied above in the anticipation analysis, in light of the known VEGF Trap-Eye/aflibercept sequence and structure information in the prior art; the publicly disclosed motivation to reduce injection frequency; and the reasonable

[13] Phase 2: 4 monthly injections + 1.6 as-needed injections = 5.6 injections/year. Phase 3 (VIEW1/2): 3 monthly injections + 5 "tertiary" injections = 8 injections/year.

expectation of success provided by the positive Phase 2 data.[14] Alternatively, Dixon in view of the '758 patent or Dix (which disclose the amino acid and nucleotide sequences for aflibercept that were well known to skilled artisans) render the Challenged Claims obvious.

3. No secondary considerations.

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

As an initial matter, the Challenged Claims do not require any particular levels of efficacy. Accordingly, Regeneron's allegation—asserted during prosecution (Ex.1017, '338 FH, 9/11/2015 Response, 8-9)—that the less frequent regimen of the Challenged Claims produced "unexpected results" is entirely irrelevant. *Ormco*, 463 F.3d at 1311-12; *Kao*, 639 F.3d at 1068-69. However, assuming Regeneron asserts those same statements to argue unexpected results, those arguments omitted highly

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[14] This Ground is equally applicable with any of the other references that disclose the proposed VIEW1/VIEW2 regimen: e.g., Ex.1007, Adis; Ex.1013, Regeneron (8-May-2008); Ex.1014, NCT-795; and/or Ex.1015, NCT-377.

pertinent information. (Ex.1017, '338 FH, 9/11/2015 Response, 7-9). ***First***, Regeneron alleged that the VIEW1/VIEW2 regimen in Example 4, as disclosed in Heier-2012 (Ex.1018, 2537), yielded unexpected results. (Ex.1017, '338 FH, 9/11/2015 Response, 7). Yet, Regeneron never told the Examiner that the same dosing regimen was the subject of numerous *pre*-2011 public disclosures (e.g., Dixon, Adis, and Regeneron press releases). (Ex.1002, Albini ¶¶ 405-06).

Second, Regeneron characterized the standard of care at the time as monthly dosing, which ignored the actual practice of ophthalmologists at the time, who had begun using PRN or treat-and-extend dosing after a series of monthly loading doses. (Ex.1002, Albini ¶ 407). Regeneron's statements are also belied by its own published clinical studies reporting regimens with less frequent dosing and the approach taken by Genentech with the ranibizumab clinical trials. (E.g., SUSTAIN, PrONTO, SAILOR (PRN dosing after three monthly loading doses); EXCITE, PIER (quarterly dosing after three monthly loading doses); *see also* Ex.1030, Mitchell, 6-7 (providing a summary of the above studies); Ex.1048, Lucentis, 1 ("treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible"); Ex.1002, Albini ¶ 408).

Third, there is nothing unexpected about the every-eight-week results in light of the Phase 2 results obtained by Regeneron—results that were omitted from their arguments to the Examiner. Phase 2 data showed mean visual acuity gains of nine

letters and a mean decrease in retinal thickness of 143 μm using a regimen that resulted in fewer average doses than their Phase 3 every-eight-week regimen. (Ex.1006, Dixon, 1576). From this, Regeneron announced in prior art press releases (also withheld from the Patent Office) that "an 8-week dosing schedule may be feasible." (Ex.1012, Regeneron (28-April-2008)), 1; Ex.1002, Albini ¶ 409).

Fourth, Regeneron's claims of "an infinite number of different treatment protocols" to choose from ignored the practical realities facing physicians at the time. Ophthalmologists were concerned about the frequency of monthly intravitreal injections. (Ex.1002, Albini ¶ 410). Monthly dosing would have been avoided if possible, and anything more frequent than monthly would not have been considered. Consequently, a new entrant to the anti-VEGF market naturally would have considered bi-monthly or quarterly dosing, particularly given Regeneron's pre-filing public statements that "[d]ue to its high affinity for all isoforms of VEGF-A . . . [and] long residence time in the eye . . . . VEGF Trap-Eye may be able to be dosed at a frequency less than monthly" and the Phase 2 data make an 8-week dosing schedule feasible. (Ex.1012, Regeneron (28-April-2008), 1). Lastly, the choice of three monthly loading doses was not surprising given the disclosure in the VEGF Trap-Eye VIEW references and the prevalence of that regimen in prior art anti-VEGF studies (e.g., SUSTAIN; EXCITE; PrONTO; SAILOR; and PIER (all using

three monthly loading doses, followed by extended dosing intervals); Ex.1002, Albini ¶¶ 410-11).

To the extent Regeneron argues long-felt but unmet need, it will be unable to establish a "need" or show that any such need was "long-felt." By 2009, the claimed dosing regimen was already publicly disclosed by Regeneron itself, and thus any "unmet" need had already been fulfilled well before the '338 patent was filed. (Ex.1002, Albini ¶ 412).

Should Regeneron argue that any purported commercial success of EYLEA® is pertinent to patentability, Regeneron will be unable to establish that such purported commercial success is attributable to the claimed regimens. (Ex.1002, Albini ¶ 413).

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

XII. CONCLUSION.

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

Dated: May 5, 2021

Respectfully Submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing Petitioner Mylan Pharmaceuticals Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 9,254,338 B2 and Exhibits 1001-1094 were served on May 5, 2021, via FedEx Priority Overnight on the Patent Owner at the correspondence address of record for U.S. Patent No. 9,254,338 B2 as evidenced in Public Pair:

Regeneron – Bozicevic Field & Francis LLP
201 Redwood Shores Parkway
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Redwood City, CA 94065

Regeneron Pharmaceuticals, Inc.
770 Old Saw Mill River Road
Tarrytown, NY 10591

/Paul J. Molino/
Paul J. Molino (Reg. No. 45,350)

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,904 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a).

Dated: May 5, 2021

/Paul J. Molino/
Paul J. Molino (Reg. No. 45,350)