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.: IPR2022-01225

U.S. Patent No. 10,130,681 B2
Filed: March 28, 2017
Issued: November 20, 2018
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. 10,130,681 B2

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1096	U.S. Patent No.: 10,888,601 B2 (“’601 patent”)
1097	U.S. Patent Nos. 7,303,746 B2; 7,303,747 B2; 7,306,799 B2; and 7,521,049 B2 (“Monthly-Dosing-Patents”)
1098	IPR2021-00881, Ex.2003, Lucentis (ranibizumab injection) Label, revised June 2010 (“IPR2021-00881, Ex.2003”)

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. 10,130,681 ("'681 patent") (Ex.1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc. ("Regeneron" or "PO").

I. INTRODUCTION.

The Challenged Claims mimic those in Regeneron's U.S. Patent No. 9,254,338 ("'338 patent") (IPR2021-00881), and like those claims, never should have issued. They are drawn to "VEGF Trap-Eye" dosing regimens well known to the person of ordinary skill in the art (hereafter, "POSA") long before January 2011. Regeneron's age-related macular degeneration ("AMD") Phase 3 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 POSAs as early as 2008. Aware of these invalidating disclosures, Regeneron sought to distinguish the Challenged Claims by incorporating a subset of the VIEW trials' "exclusion criteria," but, as discussed herein, the added elements do not save the Challenged Claims from the prior art, which renders them 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") and extensively disclosed in the prior art, including in each of Petitioner's asserted references. The amino acid and nucleotide sequences of VEGF Trap-Eye were independently disclosed and patented (*see* Ex.1008; Ex.1009; Ex.1010) well before the alleged priority date.

The VIEW1/VIEW2 clinical trials—including the VEGF Trap-Eye dosing regimens used therein—were widely published in numerous, fully-enabled prior art references. These publications disclosed *all* elements of the dosing regimen(s) in the Challenged Claims—most notably, administering three monthly loading doses followed by additional bi-monthly (*i.e.*, every-8-week) doses. Moreover, the "exclusion criteria" recited in the Challenged Claims are not entitled to patentable weight as such are widely-known requirements of the claimed and prior art dosing regimens. Notwithstanding, the VIEW1/VIEW2 clinical trials incorporated such exclusion criteria, and therefore, the added claim elements are inherently disclosed in Petitioner's asserted prior art.

Obviousness. The Challenged Claims are also invalid as obvious. As stated, the dosing regimen and exclusion criteria elements were all disclosed, either expressly or inherently, in Petitioner's asserted prior art—e.g., the recited exclusion

criteria reflect general intravitreal injection guidelines and are nearly identical to those used in the Lucentis (ranibizumab) clinical trials. In addition, prior to January 2011, the VEGF Trap-Eye amino acid sequence (claim 1, 3rd wherein clause) and nucleic acid sequence (claim 14, 3rd wherein clause) were already patented, known, and widely disclosed to POSAs.

Separately, prior to January 2011, POSAs were strongly motivated to pursue anti-VEGF dosing schedules that were less frequent than monthly administration. In particular, the prior art extensively demonstrates the various burdens of monthly intravitreal injections to treat angiogenic eye disorders. (*See, e.g.*, Ex.1006, 1574). Combined with the abundance of positive, prior art data from Regeneron's clinical trials, a POSA would have reasonably expected success at treating angiogenic eye disorders with the claimed dosing regimens.

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

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 ("RPIs") to the current Petition. Momenta Pharmaceuticals, Inc. and Janssen Research & Development LLC are wholly-owned subsidiaries of Johnson & Johnson, a publicly held company. Momenta Pharmaceuticals, Inc., Janssen Research & Development LLC,

and Johnson & Johnson are also RPIs 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)).

In May 2021, Petitioner filed petitions requesting IPR of two patents in the same family as the '681 patent. U.S. Patent No. 9,669,069 and U.S. Patent No. 9,254,338 are the subject of IPR2021-00880 and IPR2021-00881, respectively. The Patent Trial and Appeal Board ("Board") granted those petitions. (IPR2021-00880, Paper 21 (Nov. 10, 2021); IPR2021-00881, Paper 21 (Nov. 10, 2021). Both of those proceedings are currently pending before the Board, with a final written decision expected in the November, 2022 timeframe.

Petitioner is concurrently requesting IPR of U.S. Patent No. 10,888,601, which is also in the same family as the '681 patent.

To the best of Petitioner's knowledge, the following are judicial or administrative matters that would affect, or be affected by, a decision in this proceeding: *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.) and *Horizon Healthcare Servs., Inc. v. Regeneron Pharms., Inc.*, No. 1:22-cv-10493-FDS (D. Mass.). Petitioner further identifies *Chengdu Kanghong Biotechnology Co. v. Regeneron Pharms., Inc.*, No. PGR2021-00035 (P.T.A.B.).

U.S. Patent Nos. 9,254,338 B2; 9,669,069 B2; 10,857,205 B2; 10,828,345 B2; 10,888,601 B2; and 11,253,572 B2; and U.S. Patent Application Nos. 17/072,417; 17/112,063; 17/112,404; 17/350,958; and 17/740,744 each claim the benefit of the '681 patent's purported priority 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).

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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, Heinz J. Salmen, and Eric R. Hunt 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 '681 patent—which issued on November 20, 2018—is available for IPR and that Petitioner is not barred or estopped from requesting IPR of the Challenged Claims on the grounds identified herein. Neither Petitioner nor any RPI has filed a civil action challenging the validity, or been served with a complaint alleging infringement, of the '681 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. 35 U.S.C. § 325(d) DISCRETIONARY DENIAL IS UNWARRANTED.

Any argument that Petitioner's grounds or asserted prior art are cumulative of the '681 patent's prosecution should be rejected. As set forth below, the record confirms that the Examiner either (1) was not presented with the same or substantially the same art or arguments as Petitioner's, or (2) materially erred in allowing the Challenged Claims. *Advanced Bionics, LLC v. Med-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, 2020 WL 740292, at *3-4

(P.T.A.B. Feb. 13, 2020) (precedential) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (P.T.A.B. Dec. 15, 2017)).

***Becton, Dickinson* Factors (a) and (b).** Neither "the same [nor] substantially the same" art or arguments were previously presented to the Office during prosecution of the Challenged Claims. PO will likely argue that Dixon, NCT-795, and NCT-377 were submitted to the Office and marked "considered" by the Examiner. First, with respect to Dixon, the intrinsic record confirms, as the Board in IPR2021-00880 held, that "the disclosure[s] of Dixon that form the basis of Petitioner's Grounds…were not before the Examiner as prior art during examination (because the relevant disclosures were missing or omitted)." IPR2021-00880, Paper No. 21, 13, 10-13 (explaining that PO disclosed only a one-page version of Dixon to the Examiner and thus "[i]t would consequently have been impossible for the Examiner to analyze the limitations of the challenged claims in view of the complete teachings of Dixon").[1] Moreover, as set forth in more detail below, Dixon provides extensive disclosures that do not appear in any of the art before the Examiner.

[1] The '681 patent is a direct continuation of the '069 patent. (Ex.1001, Cover Page). During prosecution, PO incorporated by reference its disclosures from the '069 patent prosecution, telling the Examiner that "[a]ll of the references identified herein

Second, although PO identified NCT-795 and NCT-377 on an IDS along with over 50 other references, neither were cited or relied upon by the Examiner.[2] Indeed, the only fact PO can point to is that Dixon (one page), NCT-795, and NCT-377 were disclosed; however, "[t]he Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, 62 (P.T.A.B. Aug. 30, 2019) (citing *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, Paper 8, 40 (P.T.A.B. Nov. 7, 2018); *Amazon.com, Inc. v. M2M Solutions LLC*, IPR2019-01205, Paper 14, 16 (P.T.A.B. Jan. 27, 2020). In short, Petitioner's asserted art was neither "involved" nor "evaluated" during prosecution, and therefore, the prior art herein is not substantially the same as that previously

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were disclosed in parent application serial number 14/972,560, and as such, only a copy of non-publication number (2) is attached." (Ex.1017, 5/26/2017 Transmittal Letter, 1). In other words, only the one-page version of Dixon was disclosed to the '681 patent Examiner. IPR2021-00880, Paper No. 21, 10-13.

[2] While IDS's were marked "considered," there is no evidence regarding the *extent* the Examiner considered NCT-795 and NCT-377 or whether the Examiner appreciated or understood their disclosures' relevance to the claims.

considered by the Office. *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. § 325(d).

Becton, Dickinson* Factor (d).** Additionally, there is no overlap between Petitioner's arguments and those made during prosecution. None of Petitioner's grounds rely on prior art that was actually applied against the claims or discussed by the Examiner. *Amazon.com*, IPR2019-01205, Paper 14, 16 (finding that "a reference that 'was neither applied against the claims nor discussed by the Examiner' does not weigh in favor of exercising the Board's discretion under § 325(d) to deny a petition.")). More specifically, not one VIEW prior art reference (e.g., Dixon, NCT-795, or NCT-377) was applied against the pending claims or discussed by the Examiner. In fact, the Examiner did not assert any § 102 or § 103 rejections. (Ex.1017). Instead, the Examiner asserted obviousness-type double patenting (OTDP) rejections (based upon Regeneron's earlier sequence patents) before allowing the claims, and therefore, there is no evidence to suggest Dixon (one-page version), NCT-795 or NCT-377 were substantively considered. (Ex.1017). In response to the OTDP rejections, Regeneron relied on ***post-art disclosures of VIEW every-8-week dosing (Heier-2012), but withheld from the Examiner that the same regimen was disclosed in numerous prior art references. (Ex.1017, 6/25/2018 Remarks, 8-11).

***Becton, Dickinson* Factors (c), (e), (f): Alternatively, The Examiner Erred.** As explained above, the answer to *Advanced Bionics*' first inquiry—whether the same or substantially the same art or arguments were previously presented to the Office—is a definitive "no." Accordingly, an allegation of Examiner error is unnecessary. Nonetheless, to the extent the Board disagrees and determines *Becton, Dickinson* factors (a), (b), and (d) are satisfied with respect to Dixon, NCT-795, and/or NCT-377, discretionary denial still is not warranted because the Examiner must have therefore overlooked each reference's anticipatory disclosures, constituting material error. *Advanced Bionics*, IPR2019-01469, Paper 6, 10 (listing silence as evidence of error). As stated above and in more detail below, Dixon, NCT-795, and NCT-377 disclose, either expressly or inherently, every element of the Challenged Claims. Consequently, the Examiner should have (at least) rejected the pending claims under §§ 102, 103.

Petitioner's Additional Evidence and Arguments. Finally, the Examiner did not have the benefit of the additional evidence and arguments Petitioner presents to the Board, further weighing against § 325(d) denial. For example, Petitioner provides expert declarations (Ex.1002; Ex.1003) that set forth the POSA's understanding of the prior art disclosures. *Guardian Indus. Corp. v. Pilkington Deutschland AG*, IPR2016-01635, Paper 9, 9-10 (P.T.A.B. Feb. 15, 2017); *Taro Pharms. U.S.A., Inc. v. Apotex Techs., Inc.*, IPR2017-01446, 2017 WL 6206129, at

*8 (P.T.A.B. Nov. 28, 2017) (declining to deny petition under § 325(d) where petitioner presented new declaration evidence); *Tandus Flooring, Inc. v. Interface, Inc.*, IPR2013–00333, 2013 WL 8595289, at *2 (PTAB Dec. 9, 2013) (Paper 16) (same).

Petitioner also asserts six additional references never submitted (nor considered) during prosecution that provide additional, non-cumulative disclosures: Adis, Regeneron (8-May-2008), '758 patent, Dix, Rosenfeld-2006, and Heimann-2007. Likewise, Petitioner's anticipation and obviousness arguments were not considered by the Examiner. In sum, the '681 patent claims would not have been allowed had the Office considered the evidence and arguments presented herein.

VII. OVERVIEW OF PETITIONER'S CHALLENGES AND REQUESTED RELIEF.

A. STATUTORY GROUNDS OF CHALLENGE.

The following references anticipate the Challenged Claims:

Ground	Proposed Rejections (35 U.S.C. § 102)
1	Dixon
2	Adis
3	Regeneron (8-May-2008)

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

Ground	Proposed Rejections (35 U.S.C. § 103)
4	Dixon alone or in view of the ’758 patent and/or the ’173 patent
5	Dixon in combination with Rosenfeld-2006, and if necessary, the ’758 patent and/or the ’173 patent
6	Dixon in combination with Heimann-2007, and if necessary, the ’758 patent and/or the ’173 patent

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

VIII. OVERVIEW OF THE ’681 PATENT.[3]

The ’681 patent confirms angiogenic eye disorders, such as AMD, were known to be effectively treated through vascular endothelial growth factor

[3] Solely for this IPR, Petitioner assumes a January 13, 2011 priority date. Petitioner reserves all rights to challenge that date. The ’681 patent is subject to the AIA given the inclusion of new matter in the Continuation-In-Part Application No. 13/940,370, now the ’338 patent, filed July 12, 2013 (*see* IPR2021-00881).

("VEGF")[4] inhibition. (Ex.1001, 1:27-55). Indeed, prior to January 2011, ranibizumab (LUCENTIS®), an anti-VEGF agent, was FDA-approved for monthly administration via intravitreal injection to treat angiogenic eye disorders, including AMD. (*Id.*, 1:52-55; Ex.1048, 1). However, despite being approved for monthly dosing, ranibizumab was often administered on a *pro re nata* ("PRN" or "as needed") basis. Indeed, Genentech's ranibizumab clinical trials tested extended dosing, including PRN, and established that such regimens could achieve similar outcomes with fewer injections than monthly dosing. (Ex.1030, 1, 5).

Bevacizumab (AVASTIN®), another prior art anti-VEGF agent, has never been FDA approved for ocular indications, but has been used off-label to treat angiogenic eye disorders since long before January 2011. (Ex.1002, ¶64). Bevacizumab (AVASTIN®) is also most often administered on an as-needed (PRN) basis to treat angiogenic eye disorders. (Ex.1047, 8; Ex. 1039, 24-25). Notwithstanding, the '681 patent purports a need in the art for regimens that allow less frequent dosing. (Ex.1001, 1:56-62).

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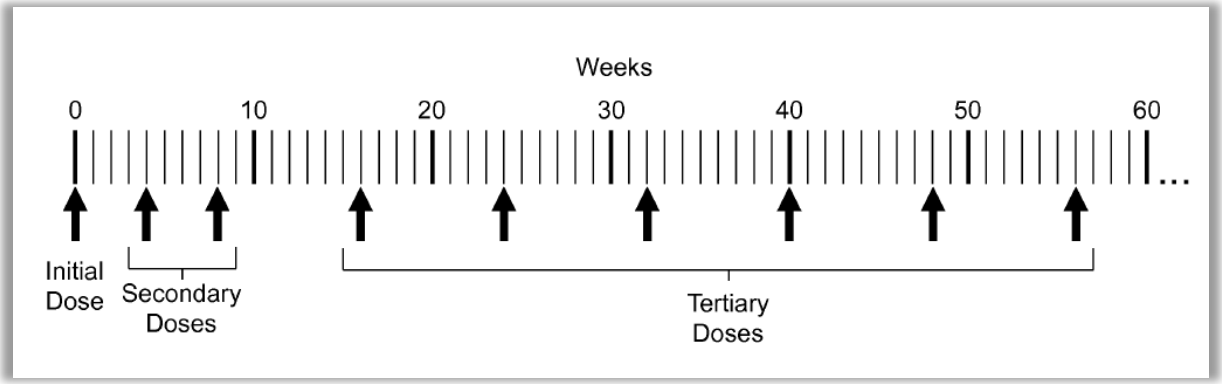
[4] VEGF is a "naturally occurring glycoprotein in the body that acts as a growth factor for endothelial cells." (Ex.1011, 711; Ex.1043, 627-28 (VEGF-A activity linked to ocular diseases, e.g., AMD).

The ’681 patent broadly claims dosing regimens for treating angiogenic eye disorders, including AMD, in patients not meeting any of three exclusion criteria: **(i)** active intraocular inflammation, **(ii)** active ocular or periocular infection, or **(iii)** ocular or periocular infection within two weeks prior to treatment, 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. (*Id.*, 21:40-63 (Claim 1)). The ’681 patent also specifically claims the prior art VIEW1/VIEW2 regimen, which eventually became FDA-approved for EYLEA® (*i.e.*, VEGF Trap-Eye/aflibercept). (*Id.*, 3:60-67, 22:39-44, 23:28-24:2). The ’681 patent also claims variations of three of the thirty-seven exclusion criteria for the prior art VIEW1/VIEW2 clinical trials: “18. Active intraocular inflammation in either eye. 19. Active ocular or periocular infection in either eye. 20. Any ocular or periocular infection within the last 2 weeks prior to Screening in either eye.” (*Id.*, 11:38-41, 21:58-62; *id.*, 10:58-12:15). The exclusion criteria are mentioned only once in the specification (Example 4). (*Id.*, 9:14-13:59).

This VIEW1/VIEW2 dosing regimen is described in the specification as “an exemplary dosing regimen of the present invention” and is depicted graphically as follows:



(*Id.*, (Fig.1), 4:2-4, 2:55-62). The Figure, in combination with the three exclusion criteria listed above, illustrates and exemplifies a dosing regimen falling within the Challenged Claims.

During prosecution, PO argued, in response to OTDP rejections, that the (then-pending) claims were patentably distinct from its Monthly-Dosing Patents[5] on the ground that those did not disclose the claimed regimen. (Ex.1017, 6/25/2018 Remarks, 7). PO further argued once-per-month dosing represented the standard of care for treatment of AMD at the time of the invention and that the pending claims were distinct because an infinite number of other treatment protocols could have been considered. (*Id.*, 7-11; Ex.1018, 2537).

[5] 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.1097; Ex.1017, 4/3/2018 Office Action, 3-6).

PO 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 as needed (PRN)) for the effective treatment of diabetic macular edema (DME)." (Ex.1017, 6/25/2018 Response, 10). One Example 5 dosing regimen is identical to the prior art VIEW1/VIEW2 regimen for AMD. The Example 5 Phase 2 DME dosing regimens also were disclosed before January 2011. (Ex.1068, 1).

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

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

A. "A METHOD FOR TREATING AN ANGIOGENIC EYE DISORDER IN A PATIENT."

1. The "method for treating" preamble is not a limitation 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[6] 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 Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (preamble 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 PO asserted the preamble to traverse any Examiner rejections. (*See, e.g.*, Ex.1017, 6/25/18 Remarks, 7-11).

Moreover, PO's reliance on alleged "unexpected results" during prosecution does not render the preamble 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); *Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, No. IPR2016-00712, 2016 WL

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

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).

For these reasons, Petitioner submits that the preamble is non-limiting and no construction is necessary.

2. PO's anticipated argument that the preamble is a positive limitation should be rejected.

In related proceedings, PO has argued that analogous preambles (in patents within the same family) are positive claim limitations but PO provides a variety of proposals for that same term:

- "a therapeutically effective method," (PGR2021-00035, Paper 6, 7);
- "an effective method of treatment," (IPR2021-00881, Paper 10, 36);
- "a high level of efficacy that is not inferior to the existing standard-of-care," (IPR2021-00881, Paper 41, 12); and
- "Regeneron does not advance claim construction positions for these terms," (IPR2021-00880, Paper 10, 19).

It remains to be seen which of these approaches PO will assert here, or if they will submit something new. Regardless, any attempt to read efficacy limitations into the preamble 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, 13:15-34 (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 *intended* purpose, and therefore, not a limitation. *Bristol-Myers*, 246 F.3d at 1375; *Copaxone*, 906 F.3d at 1022-23.

Second, the preamble provides no antecedent basis for any other claim element, and any argument that "the patient" and "angiogenic eye disorder" claim terms 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 constitute a positive limitation.

For at least the above reasons, Petitioner submits no construction of the preamble is necessary.

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

If the Board finds it a limitation, the preamble should be construed to have its plain and ordinary meaning—namely, "administering a therapeutic to a patient,

without a specific degree of efficacy required."

In the context of the '338 patent, the Board preliminarily found "that the preambles of the independent claims do not require the recited method steps to provide an *effective* treatment." (IPR2021-00881, Paper 21, 21). In so finding, the Board rejected Regeneron's arguments to the contrary, noting that "Patent Owner does not direct us to any other portion of the claims or written description in the '338 patent that supports finding that the claimed method for treating an angiogenic eye disorder requires such treatment method to have any particular level of effectiveness." (*Id.*, 20). Not only does the '681 patent share the same specification as the '338 patent, but the '681 patent claims also are identical to the '338 patent claims, adding only the "wherein exclusion criteria" element—which also does not lend any particular level of efficacy to the claimed method. Consequently, Regeneron's arguments similarly fail here. *See 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."). If limiting, the preamble 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.

PO's anticipated proposed construction—"a high level of efficacy that is not inferior to the existing standard-of-care" (IPR2021-00881, Paper 41, 12)—lacks support in the intrinsic record and thus should be rejected.[7] Indeed, reading-in a "high level of efficacy" here would be committing "one of the cardinal sins of patent law." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001); *Copaxone*, 906 F.3d at 1023. Indeed, the intrinsic record states that "beneficial therapeutic effects ***can be*** achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist"—not "must be" achieved. (Ex.1001, 2:7-12 (emphasis added); IPR2021-00881, Paper 21, 21). For example, the specification states "a dosing regimen of the present invention is shown in [Figure 1]" (Ex.1001, 2:17-18), which illustrates *only* the temporal dose sequence, no efficacy outcomes.

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[7] There are no data in the '681 patent setting forth the non-inferiority to any so-called, undefined "standard of care" for any of the other angiogenic eye disorders listed in the patent. (Ex.1001, 5:14-32). Even for AMD, PO admitted that AMD patients were excluded from the VIEW study (IPR2021-00881, Paper 41, 43-46), meaning no non-inferiority data exist for those patients.

Second, under PO's anticipated construction, a POSA is only able to determine infringement (or not) *retroactively*. Specifically, a POSA, treating a patient, can only determine whether or not that treatment infringed after-the-fact by exhibiting a "high degree of efficacy" that was "non-inferior to the existing standard-of-care."[8] Such a construction undermines the patent's notice function.

Third, PO's anticipated "high level of efficacy" construction generates § 112 enablement, written description, and definiteness problems, because the specification provides no means or parameters for ascertaining what constitutes a "***high*** level of efficacy." (Ex.1002 [Albini decl.], ¶¶48-52); *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999) (constructions rendering claims invalid or meaningless should be avoided). The same is true of PO's "not inferior to the existing standard-of-care." PO's so-called "standard-of-care" is specific to each angiogenic eye disorder being treated and may further vary with respect to time, patient, and treating physician. (Ex.1002, ¶¶48-51). Accordingly, PO's anticipated proposal opens the claims to a near-infinite level of variability and subjectivity, and therefore, cannot be correct.

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[8] Non-inferiority is a population-based clinical trial statistical determination. There is no support in the specification describing how to assess whether the treatment of the claimed *single patient* is "not inferior to the existing standard-of-care."

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

The Challenged Claims recite "initial dose," "secondary dose," and "tertiary dose." A POSA would understand each as expressly defined in the 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.

(Ex.1001, 3:34-41; Ex.1002, ¶44-45). 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, 3:54-59; Ex.1002, ¶44-45). 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)."

In the -881 IPR, the Board agreed with Petitioner: "Based on those express definitions, we do not find cause to construe the terms differently." (IPR2021-00881, Paper 21, 23). In so finding, the Board rejected PO's contradictory

arguments: "In particular, we do not find that the Specification requires the 'tertiary doses' to maintain any efficacy gain achieved after the initial and secondary doses, or that the term 'connotes a specific level of efficacy' for the reasons urged by Patent Owner." (*Id.*) As the '681 patent shares the same specification as the '338 patent (and the claims are identical but for the "exclusion criteria" clause), PO's arguments should similarly fail here. *See Samsung Elecs.*, 925 F.3d at 1378.

C. "WHEREIN EXCLUSION CRITERIA FOR THE PATIENT INCLUDE ALL OF…"

The Challenged Claims recite three exclusion criteria:

> wherein exclusion criteria for the patient include all of:
> (1) active intraocular inflammation;
> (2) active ocular or periocular infection;
> (3) any ocular or periocular infection within the last 2 weeks prior to treatment.

(Ex.1001, 21:58-63; *id.* 23:19-23). For the following reasons, "exclusion criteria" should not be treated as a limitation on the Challenged Claims.

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

Determining whether a claim limitation is entitled to patentable weight under the printed matter doctrine is a two-step process. The first "is the determination that the limitation in question is in fact directed toward printed matter." *In re Distefano*, 808 F.3d 845, 848 (Fed. Cir. 2015). A claim limitation need not literally be directed to "printed" materials; rather, "a claim limitation is directed to printed matter 'if it

claims the content of information.'" *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018) (quoting *In re DiStefano*, 808 F.3d at 848). The second "is to ascertain whether the printed matter is functionally related to" the rest of the claim. *Id.*

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

The "Exclusion Criteria" Limitation Is Directed Toward Printed Matter. In the '681 patent, the "exclusion criteria" (*i.e.*, preexisting conditions) represent informational content regarding the patient, and therefore, should be considered "printed matter" that are accorded "no patentable weight." Like the "elect[ing]" step

in *Praxair Distribution*, no active step of applying (or assessing the patient for) the "exclusion criteria" in the Challenged Claims, is sufficient to impart patentability to that mental step/printed material element. Even assuming that application of the "exclusion criteria" could be inferred, the Challenged Claims do not dictate that any step be taken or that any alteration be made to the claimed dosing regimen.

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

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

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

To the extent PO argues that whether the "exclusion criteria" are unpatentable mental steps is a determination under 35 U.S.C. § 101, PO is mistaken. The Board's application of the printed matter doctrine to the "exclusion criteria" is an effort to define the scope and meaning of specific claim terms, and whether the "exclusion

criteria" element "will not distinguish the invention from the prior art in terms of patentability" under an anticipation or obviousness analysis. *In re Gulack*, 703 F.2d 1381, 1385 (Fed. Cir. 1983); *Praxair Distribution*, 890 F.3d at 1033 ("The printed matter doctrine thus raises an issue where the § 101 patent-eligibility inquiry and the § 102 and § 103 novelty and nonobviousness inquiries overlap.").

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

X. PERSON OF ORDINARY SKILL IN THE ART.

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

medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists. (Ex.1002, ¶¶27-29; Ex.1003, ¶¶21-25; *see* IPR2021-00881, Paper 21, 16 ("Petitioner's definition of one of ordinary skill in the art is reasonable and consistent with the '338 patent and the prior art of record")).

XI. TECHNOLOGICAL BACKGROUND AND PRIOR ART SCOPE.

Publications below reflect anticipatory disclosures of the subject matter in the Challenged Claims, together with knowledge that POSAs 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 POSA 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.

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, 11394 (Fig.1A)). The terms aflibercept and VEGF Trap-Eye were known in the art to refer to the same

active ingredient. (Ex.1006, 1573 ("***One*** promising new drug is aflibercept (VEGF Trap-Eye), ***a*** fusion protein…." (emphasis added), 1575 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure"); Ex.1007, 261 ("Aflibercept…VEGF Trap-Eye"; "Aflibercept is in clinical development…for the treatment of cancer, while Regeneron and Bayer are developing the agent for eye disorders."), 263 ("The VIEW2 trial…will evaluate the safety and efficacy of aflibercept"); Ex. 1002, ¶¶83-86, 102-03).

Regeneron confirmed in submissions to the Patent Office that (1) aflibercept and VEGF Trap-Eye were synonymous; (2) the construction of VEGF Trap-Eye/aflibercept was described in Holash; and (3) the sequence of VEGF Trap-Eye/aflibercept was set forth in Regeneron's prior art '758 and '959 patents. (Ex.1024, 2, 6-7; Ex.1023, 2, 5-7 ("The nucleic acid and amino acid sequence of VEGFR1R2-FcΔC1(a) is provided in Figures 24A-C…. Thus aflibercept is a fusion protein encoded by a nucleic acid sequence of SEQ ID NO: 15."; "aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP$_{R1R2}$")). Regeneron also represented to the Patent Office that the VIEW clinical trials correspond to Example 4 of the '681 patent—in other words, the same trials, and the same molecule, disclosed in Petitioner's art (e.g., Dixon, etc.). (Ex.1017, 6/25/2018, Remarks, 9).

Regeneron publications also made it clear that VEGF Trap-Eye and

aflibercept referred to the same agent, whose construction was described in Holash, and whose sequence was set forth in numerous Regeneron publications and the 2006 WHO Drug Information publication. As discussed, Holash described the construction of the molecule. (Ex.1004, 11393-94, Fig. 1 ("VEGF $Trap_{R1R2}$ possesses the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc portion of human IgG1.")).

Numerous post-Holash publications discussing both aflibercept and VEGF Trap-Eye cite back to Holash. (Ex.1026, 18363, 18370 (discussing VEGF Trap, including "aflibercept" as a keyword, and citing back to Holash (ref. 20)); Ex.1028, 2 (discussing VEGF Trap-Eye while citing back to Holash, and discussing the data presented therein for VEGF $Trap_{R1R2}$); Ex.1029, 940, 945 ("a new anti-VEGF agent, VEGF Trap/aflibercept (henceforth referred to as VEGF Trap), has been developed by incorporating domains of both VEGF receptor 1 (VEGFR-1) and VEGFR-2 fused to the constant region of human immunoglobulin G1," and citing Holash); Ex.1031, 1009-10 (discussing VEGF Trap-Eye and its structure, and citing back to Holash); Ex.1036, 4414, 4420 ("To block VEGF, we employed the VEGF Trap (aflibercept) (Regeneron Pharmaceuticals), a recombinant chimeric protein comprising portions of the extracellular domains of the human VEGF receptors 1 and 2 expressed in sequence with the Fc portion of human Ig.") (citing Holash)).

Regeneron's patents confirm the identity of VEGF Trap-Eye/aflibercept. For

example, Regeneron's prior art '173 patent discloses that "[i]n a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF $trap_{R1R2}$)" and discloses a specific sequence. (Ex.1008, 1:48-52). Interested POSAs would have readily identified VEGFR1R2-FcΔC1(a) as having the specific sequence disclosed for it in the '173 patent, and, based on a simple alignment, would have understood it to have the same sequence as aflibercept. (Ex.1092; Ex.1093). A POSA further would have understood the VEGF $Trap_{R1R2}$ nomenclature to reference the single agent constructed and tested in Holash, and referenced in the numerous VEGF Trap-Eye/aflibercept references, including but not limited to those discussed above, thus tying the sequences with the nomenclature, and confirming without a doubt, the identity and sequence of VEGF Trap-Eye/aflibercept. (Ex.1002, ¶¶83-86).

VEGF Trap-Eye was developed to target angiogenic disorders, including eye disorders, such as AMD, DME, and RVO. Other anti-VEGF agents were already approved and being used (in some cases off-label) in the treatment of these disorders, including AMD.

Regeneron placed VEGF Trap-Eye into clinical studies in the mid-2000's. (Ex.1005, 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

the results of its Phase 2 trial, CLEAR-IT-2, assessing PRN dosing after 4 monthly loading doses. (Ex.1012; Ex.1013). Regeneron also announced initiation of its Phase 3 VIEW clinical trials assessing every-8-week dosing, the same clinical trials discussed in Dixon and Adis. (Ex.1012; Ex.1013; Ex.1006; Ex.1007). The publicly disclosed prior art dosing regimen of the VIEW clinical trial is the same dosing regimen Regeneron later claimed in the '681 patent.

B. EXCLUSION CRITERIA.

Historically, certain patient populations, such as those with pre-existing conditions, were excluded from anti-VEGF therapy treatment. (Ex. 1002, ¶¶93-98). For example, the LUCENTIS (ranibizumab) clinical trials employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis (inflammation) in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (Ex.1037, 62; Ex.1048, 2 ("LUCENTIS is contraindicated in patients with ocular or periocular infections."); Ex. 1002, ¶¶94-97, 135-36; *compare with* Ex.1001, Claim 1). Such exclusion criteria were also employed in VIEW1/VIEW2. (Ex.1018, Appx. 2, 2,3). It was therefore understood that some patients should be excluded from intravitreal injection treatment, particularly those at increased risk for infection and/or inflammation. (Ex.1040, 76 (reporting that "[p]atients with acute or chronic infections of the anterior segment

and ocular adnexa, e.g., conjunctivitis or blepharitis, should first undergo treatment of the infectious diseases before proceeding to the injection"), 81 (concomitant eye diseases such as "[b]acterial infections should be treated before performing an intravitreal injection"; "rule out possible contraindications…that might complicate the injection"), 85 ("[e]xclude patients with suspected bacterial infections or the anterior segment (e.g., blepharitis, conjunctivitis)"); Ex. 1002, ¶93). Moreover, it was known that intravitreal injections presented further complications for such patients. (Ex.1006, 1577 ("Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis"); Ex.1057, 677 ("Several potential complications of IVT injection, such as endophthalmitis…can be vision threatening."); Ex.1040, 67, 69, 74-75; Ex.1018, Heier-2012, 2537; *see* Ex. 1002, ¶¶91, 138-39).

The POSA would have further understood that the leading AMD treatment at the relevant time—LUCENTIS (ranibizumab)—was contraindicated in patients with ocular or periocular infections. (Ex.1098, 2; Ex. 1002, ¶94). A POSA also would have understood that a meaningful head-to-head statistical comparison of the VIEW aflibercept arms with monthly ranibizumab and the outcomes of the MARINA and ANCHOR trials would necessitate having a very similar patient population in the VIEW trials. A clinical study designer/investigator would understand that the way to do this is to adopt the same, or very similar, exclusion/inclusion criteria as those

used in the comparator study, in this case MARINA and ANCHOR. (Ex.1018, Heier-2012, 2540 ("[i]nclusion and exclusion criteria were designed to maintain consistency with the pivotal trials for the reference drug ranibizumab, consistent with regulatory guidelines for noninferiority studies"); Ex. 1002, ¶¶97, 351).

C. PETITIONER'S PRIOR ART REFERENCES.[9]

The following clinical trials are disclosed in Petitioner's prior art and are summarized here for the Board's convenience:

[9] The asserted prior art references all qualify as publications that were available to—and indeed cited by—interested POSAs before the '681 patent's earliest, purported priority date (i.e., January 13, 2011). (Ex.1003, Gerritsen ¶¶46-57, 78-92; Ex.1006, 1579 (citing NCT Studies); Ex.1007, 268 (citing Regeneron Press Releases)).

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)	Three monthly doses, followed by bi-monthly (*i.e.*, every-8-week) doses (2 mg)

The VIEW1/VIEW2 dosing regimen involved an "initial dose" (day 0); two "secondary doses" (weeks 4 and 8); followed by "tertiary doses" administered every eight weeks thereafter. (Ex.1002, ¶¶88, 90, 108, 115, 120, 126, 146-47, 152, 158, 166, 179, 199, 210-11, 235, 246, 255, 258, 286, 301, 395).

1. Dixon (Ex.1006).

Dixon published in 2009 and thus constitutes prior art under 35 U.S.C. § 102. As set forth above (Section VI), Dixon—in its entirety—was neither submitted nor cited during prosecution, and thus never considered by the Examiner. IPR2021-00880, Paper No. 21, 10-13. PO has not contested Dixon's status as prior art in related proceedings IPR2021-00880 and -881. *Regeneron Pharms., Inc. v. Novartis Pharma AG*, IPR2021-00816, Paper No. 1, 23 (Apr. 16, 2021) ("Dixon was publicly accessible in print by October 2009, and online by August 20, 2009.").

Dixon discloses that in the context of AMD treatments, "[o]ne promising new drug is aflibercept (VEGF Trap-Eye)." (Ex.1006, 1573 (disclosing VEGF Trap-Eye/aflibercept as "a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2")). Dixon teaches that VEGF Trap-Eye is an "anti-VEGF therapy, with Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Ex.1006, 1573). Dixon also discloses VIEW1/VIEW2 and the dosing regimens used therein. (*Id.*, 1573, 1575-76, 1579 (Bibliography Nos. 46-47); Ex.1002, ¶¶88, 108, 146-47; Ex.1003, Gerritsen ¶90).

Dixon notes the "time and financial burden of monthly injections" led researchers "to examine the efficacy of alternative dosing schedules." (Ex.1006, 1574). Identifying the problem of the "significant time and financial burden [that]

falls on patients during their treatment course" of monthly injections of drugs such as ranibizumab, and the desirability of "decreased dosing intervals," Dixon reports that "[t]he development of new drugs for neovascular AMD has thus focused on both improving efficacy and extending duration of action." (Ex.1006, 1574, 1577; Ex.1002, ¶¶105, 298).

Dixon discloses how the VIEW1/VIEW2 dosing regimens fall squarely within the scope of the Challenged Claims:

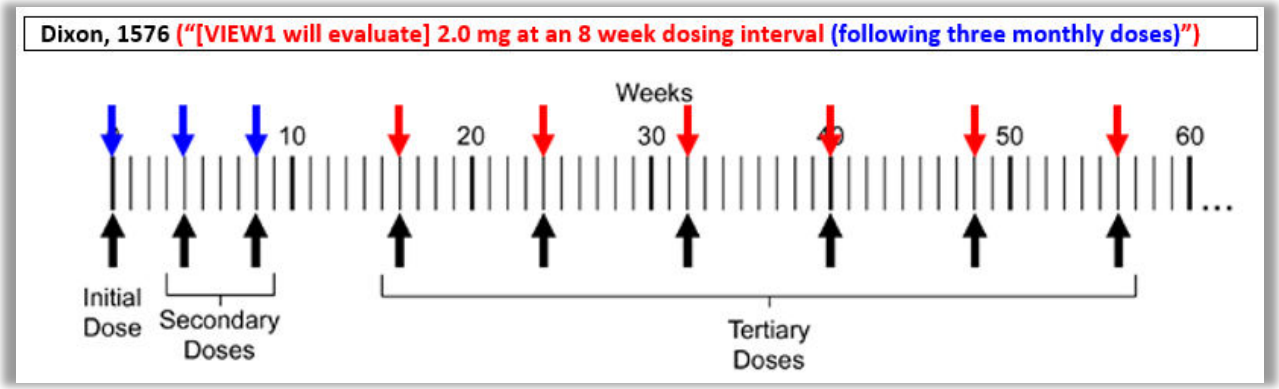

Figure 1. (Modified from Fig.1 of the '681 patent).

Dixon's disclosure of an "8 week dosing interval (following three monthly doses)," means that three monthly doses (**blue arrows**) were to be administered, followed by injections at eight week intervals thereafter (**red arrows**). (*See* Ex.1006, 1576; Ex.1002, ¶¶108, 147, 155, 183). PO has not disputed this Dixon disclosure in related proceedings IPR2021-00880 and -881.

Dixon also discloses the promising results of CLEAR-IT-2, 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 (9.0) letters and a mean decrease in retinal thickness of 143 μm. (Ex.1006, 1576; Ex.1002, ¶¶106-07). Importantly, patients that received monthly loading doses required on average, *only 1.6 more injections* for the remainder of the year. (Ex.1006, 1576; Ex.1002, ¶¶107, 302, 354).

Additionally, Dixon discloses that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure" but differ in purification and formulation. (Ex.1006, 1575, 1573 ("***[o]ne*** promising new drug is aflibercept (VEGF Trap-Eye)")). Accordingly, a POSA would have understood that the active ingredient was the same in both presentations. (Ex.1002, ¶¶83-86, 103). For example, in addition to Dixon's description of the agent as "***[o]ne*** promising new drug" and "***a*** fusion protein," Dixon discussed the half-lives of aflibercept in both systemic and intravitreal contexts, informing a POSA that aflibercept was the active ingredient in both oncology (where systemic administration is the norm) and eye disorder settings (where intravitreal administration is the norm). (Ex.1006, 1575 ("free aflibercept has a terminal half-life of ~17 days in the circulation. The half-life of human intravitreal doses is unknown.")).

In addition, Dixon discloses that VIEW was to be a non-inferiority study that included comparison with monthly ranibizumab. (Ex.1006, 1575).Further, Dixon discloses that "[e]ach injection subjects patients to risks of cataract, intraocular

inflammation, retinal detachment and endophthalmitis." (Ex.1006, 1577). Endophthalmitis is a serious and potentially devastating bacterial or fungal infection known to be one of the more serious adverse side effects of intravitreal injections and other invasive ocular surgical procedures. (Ex.1002, ¶¶70, 91, 310).

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, References Cited). PO has not contested Adis' status as prior art in related proceeding IPR2021-00881.

Adis is entitled "Aflibercept" and provides in the sub-title a number of other synonyms for aflibercept, including VEGF Trap-Eye. (Ex.1007, 261).

Adis discloses, *inter alia*, VEGF treatment to prevent blood vessel formation and vascular leakage associated with wet AMD. (Ex.1007, 261). Adis further states "***[a]flibercept*** is in clinical development with Regeneron Pharmaceuticals and sanofi-aventis for the treatment of cancer, while Regeneron and Bayer are developing ***the agent*** for eye disorders"—in other words, equating "aflibercept" (oncology) with "VEGF Trap-Eye" (ophthalmology). (*Id.* (emphasis added); Ex.1002, ¶113).

Adis further discloses the construction of VEGF Trap-Eye/aflibercept and the Chemical Abstracts Services ("CAS") number associated with the molecule

(862111-32-8), as well as other codes identifying the molecule as a diabetes, ophthalmological, and anti-neoplastic (*i.e.*, anti-tumor) agent. (Ex.1007, 261, 264).

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, 263; Ex.1002, ¶¶115, 196) (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, 263, 268 (Ref. Nos. 10-14); Ex.1002, ¶118).

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, 263; Ex.1002, ¶¶116-17). For example, Adis reports that, at the 32-week point, patients receiving 0.5 mg or 2.0 mg monthly loading doses followed by PRN treatment achieved 8.0 and 10.1 letters, and mean decreases in retinal thickness of 141 and 162 microns. (Ex.1007, 267). Adis also reports that, on average, patients in all dose groups, required only 1 additional injection between week 12 (the end of the loading doses) and week 32 (when results were reported), and that 55% of patients receiving 2.0 mg monthly loading doses did not require any additional treatment between week 12 and week 32. (*Id.*, 268).

Further, Adis reported results from the Phase 1 trial, which showed that, with just a single dose of aflibercept, 95% of patients exhibited stabilization or improvement in visual acuity, and patients showed "rapid, substantial and prolonged" reductions in retinal thickness. (*Id.*).

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. To Petitioner's knowledge (and as set forth above in Section VI), Regeneron (8-May-2008) was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, References Cited). PO has not contested Ex.1013's status as prior art in related proceeding IPR2021-00881.

Regeneron (8-May-2008) reports VIEW1/VIEW2 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, 1; Ex.1002, ¶¶120, 246; Ex.1003, Gerritsen ¶¶46-57, 78-80).

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, 1; Ex.1002, ¶121).

4. ’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, References Cited). PO has not contested the ‘758 patent’s status as prior art in related proceeding IPR2021-00881.

The ’758 patent is assigned to Regeneron and 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, Abstract, 19:15-17, 29:39-56). The aflibercept sequence is disclosed in Figures 24A-C. (*Compare* Ex.1001, SEQ ID NO:1 and SEQ ID NO:2, *with* Ex.1010, Fig.24A-C; Ex.1024, 2, 6-7; Ex.1002, ¶¶127, 148; Ex.1092; Ex.1093).

The ’758 patent also teaches that aflibercept may be useful for treating eye disorders such as AMD. (Ex.1010, 15:50-16:6; *id.*, 3:5-29; Ex.1002, ¶127).

5. ’173 patent (Ex.1008).

The ’173 patent issued May 12, 2009, and thus is prior art under 35 U.S.C. § 102. To Petitioner’s knowledge, the ’173 patent was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, References Cited).

The ’173 patent teaches methods of reducing angiogenesis through the

administration of a VEGF antagonist fusion protein that possesses the same sequence as the VEGF antagonist in the Challenged Claims. (Ex.1008, 1:32-56, SEQ ID NOS:1 and 2; Ex.1092; 1093).

The '173 patent further discloses that "[i]n a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap$_{R1R2}$) comprising the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQID NO: 2." (Ex.1008, 1:48-52; Ex.1002, ¶132).

6. Rosenfeld-2006 (Ex.1058).

Rosenfeld-2006 published in 2006, and thus is prior art under 35 U.S.C. § 102. To Petitioner's knowledge, Rosenfeld-2006 was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, References Cited).

Rosenfeld-2006 discloses the ranibizumab Phase 3 clinical trial, MARINA, including results thereof. (Ex.1058, 1425-27). Rosenfeld-2006 reports that ranibizumab is "a recombinant, humanized monoclonal antibody Fab that neutralizes all active forms of VEGF-A." (*Id.*, 1420).

Rosenfeld-2006 further discloses patient eligibility criteria for MARINA. (*Id.*, 1420-21). Specifically, Table 1 provides a full list of exclusion criteria, which includes, *inter alia*, the following:

- Active intraocular inflammation;

- Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis;

(*Id.*, Appx. Table 1; Ex.1002, ¶¶136, 349).

7. Heimann-2007 (Ex.1040).

Heimann-2007 published in 2007, and thus is prior art under 35 U.S.C. § 102. To Petitioner's knowledge, Heimann-2007 was neither submitted nor cited during prosecution, and thus never considered by the Examiner. (Ex.1001, References Cited).

Heimann-2007 discloses guidelines and strategies for the administration of intravitreal injections—specifically, that while adverse events are rare, "the rate can increase significantly if certain standards for intraocular interventions are not followed." (Ex.1040, 67; Ex. 1002, ¶138). Heimann-2007 discloses that "[s]everal guidelines on the technique for intravitreal injections have been published in recent years" and that "[s]trict adherence to these guidelines is advisable." (*Id.* ("[e]ndophthalmitis is the most feared complication of intravitreal injections"); Ex. 1002, ¶¶139, 348-49).

Heimann-2007 discloses numerous complications that may result from intravitreal injections, including endophthalmitis, keratitis, intraocular inflammation, and uveitis/pseudo-endophthalmitis. (*Id.*, 68 (Table 5.1), 69 (disclosing endophthalmitis as one of "[t]he most serious side effects of intravitreal injections"), 74-75 ("[o]ther important, potentially sight-threatening complications

of injections are intraocular inflammation"), 75 (uveitis and pseudo-endophthalmitis); Ex. 1002, ¶138).

Heimann-2007 discloses that "[i]nfectious endophthalmitis is the most feared complication of intravitreal injections and has been reported after application of all currently used preparations," and that its prevention is "one of the key issues" regarding intravitreal injections. (*Id.*, 76 ("[p]atients with acute or chronic infections of the anterior segment and ocular adnexa, e.g., conjunctivitis or blepharitis, should first undergo treatment of the infectious diseases before proceeding to the injection"); Ex. 1002, ¶138).

Heimann-2007 continues, noting that concomitant eye diseases, such as bacterial infections, "should be treated before performing an intravitreal injection," and that pre-operation assessments be done "to rule out possible contraindications…that might complicate the injection." (*Id.*, 81). Heimann-2007 concludes with instructions to "[e]xclude patients with suspected bacterial infections of the anterior segment (e.g., blepharitis, conjunctivitis)." (*Id.*, 85; Ex. 1002, ¶138).

XII. GROUNDS FOR UNPATENTABILITY—DETAILED ANALYSIS.

A. ANTICIPATION.

The Challenged Claims are anticipated by each of Dixon, Adis, and Regeneron (8-May-2008). 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).

A claim is inherently anticipated if "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 (*i.e.*, a temporal sequences of doses) without any particular efficacy or result (IPR2021-00881, Paper 21, 20-23; Ex.1002, ¶¶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, as shown in the following tables, and confirmed by Dr. Albini (Ex.1002, ¶¶140-52, 171-77):

Claim 1:	**Dixon:**
A method for treating an angiogenic eye disorder in a patient,	Preamble is not limiting. "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, 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). "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).
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary	"[Phase 3] will evaluate the safety and efficacy of…2.0 mg at an 8 week dosing interval (following three monthly doses)." (Ex.1006, 1576).

Claim 1:	**Dixon:**
doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	(*i.e.*, doses at week **0, 4, 8, 16, 24, 32, 40, and 48**).
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 232-457 of 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, 1576 (Fig.1)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575). "One promising new drug is aflibercept (VEGF Trap-Eye)" (*Id.*, 1573). The amino acid sequence and structural information for VEGF Trap-Eye are inherent in Dixon. (Ex.1010, Fig.24A-C, 10:15-17; Ex,1008, 1:48-52, SEQ ID NOS: 1 & 2; Ex.1002, ¶148).
wherein exclusion criteria for the patient include all of: (1) active intraocular inflammation; (2) active ocular or periocular infection; (3) any ocular or periocular infection within the last 2 weeks prior to treatment.	Not entitled to patentable weight, and thus unable to distinguish the claims from the prior art. Notwithstanding, excluding patients exhibiting the recited "exclusion criteria" was a necessary, and thus inherent outcome, of VIEW. (Ex.1018, Appx. 2-3; Ex.1001, 9:14-13:59). (Ex.1002, ¶¶149-51).

Claim 14 recites the nucleotide, as opposed to the amino acid, sequence to identify VEGF Trap-Eye/aflibercept. All other elements are the same as claim 1. The claim 14 sequence element does not distinguish it from Dixon:

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, 1576 (Fig.1)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575). "One promising new drug is aflibercept (VEGF Trap-Eye)" (*Id.*, 1573). (Ex.1002, ¶¶84, 127, 132, 148, 173).

Claims 3 and 16 further recite "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, 1576, Ex.1002, ¶¶153-56, 175-77, 151-53; Fig.1 (*supra* § XI(C)(1) (**blue arrows**))).

Claims 4 and 17 recite "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose." Dixon expressly discloses "an 8 week dosing

interval." (Ex.1006, 1576; Ex.1002, ¶¶153-56, 175-77; Fig. 1 (*supra* § XI(C)(1) (**red arrows**)); *see also* Ex.1002, ¶¶ 196, 205-08, 228-30).

Claims 5 and 19 recite "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 VIEW study continued for at least one year, (Ex.1006, 1576), which, under the proposed regimen, would yield "at least 5 tertiary doses" administered eight weeks apart. (Ex.1002, ¶¶157-59, 181-84; Fig.1 (*supra* § XI(C)(1) (**red arrows**)); *see also* Ex.1002, ¶¶ 196, 205-08, 228-30).

Claims 6, 7, 18, and 20 recite AMD. Dixon discloses administering VEGF Trap-Eye to patients with AMD. (Ex.1006, 1573, 1576 ("~1200 patients with neovascular AMD"); Ex.1002, ¶¶160-62, 178-80).

Claims 8-10 and 21-23 recite "intraocular administration" and "intravitreal administration." Intravitreal administration is a subset of intraocular administration and refers to administration directly into the vitreous of the eye. (Ex.1002, ¶¶163-67, 185-90; Ex.1001, 2:40-43). Dixon discloses "the safety and efficacy of intravitreal VEGF Trap-Eye." (Ex.1006, 1576).

Claims 11, 13, 24, and 26 recite "2 mg" of the VEGF antagonist. Dixon discloses 2.0 mg VEGF Trap-Eye doses. (Ex.1006, 1576; Ex.1002, ¶¶168-70, 191-93).

* * *

Accordingly, Dixon discloses the limitations of each Challenged Claim, and thus anticipates.

3. Grounds 2 and 3: Adis and Regeneron (8-May-2008) anticipate the Challenged Claims.

Independent Claims 1 and 14 are anticipated by Adis and Regeneron (8-May-2008), which, as shown below, and confirmed by Dr. Albini (Ex.1002, ¶¶194-204, 224-27, 245-52, 273-76), disclose each and every element:

Claim 1:	**Prior Art:**
A method for treating an angiogenic eye disorder in a patient,	Preamble not limiting. **Adis**: "Regeneron and Bayer are developing [aflibercept] for eye disorders." (Ex.1007, 261, 263). "A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008." (*Id.*, 263).
	Regeneron (8-May-2008): "Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration." (Ex.1013, 1).
said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist,	**Adis**: "[VIEW 2] will evaluate the safety and efficacy of aflibercept at…2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Ex.1007, 263).

Claim 1:	**Prior Art:**
followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	**Regeneron (8-May-2008)**: 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, 1). (*i.e.*, injections at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**).
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 232-457 of SEQ ID NO:2.	**Adis**: "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, 261 (disclosing aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye are same molecule)). **Regeneron (8-May-2008)**: "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, 2).

Claim 1:	**Prior Art:**
wherein exclusion criteria for the patient include all of: (1) active intraocular inflammation; (2) active ocular or periocular infection; (3) any ocular or periocular infection within the last 2 weeks prior to treatment.	Not entitled to patentable weight, and thus unable to distinguish the claims from the prior art. In any event, the exclusion of patients exhibiting the recited exclusion criteria was a necessary, and thus inherent outcome, of the protocol of the VIEW clinical trials disclosed in Adis and Regeneron (8-May-2008). (Ex.1018, Appendix 2, 3; Ex.1001, 9:14-13:59).

(Ex.1002, ¶¶194-204).

Claim 14 recites the nucleotide, as opposed to the amino acid, sequence to identify VEGF Trap-Eye/aflibercept. All other elements are the same as claim 1. The claim 14 sequence element does not distinguish it from Adis and Regeneron (8-May-2008):

Claim 14:	**Prior Art:**
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.	**Adis**: "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, 261).[10]
	Regeneron (8-May-2008): "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, 2).

(Ex.1002, ¶¶87, 127, 132, 148, 173, 224-27; 273-76).

Claims 3 and 16 recite "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, 263). Regeneron (8-May-2008) 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, 1; Ex.1002, ¶¶205-08, 228-30, 253-56, 277-80; Fig.1 (*supra*

[10] Adis confirms VEGF Trap-Eye and aflibercept are the same molecule. (Ex.1007, 261; Ex.1002, ¶113).

§ XI(C)(1) (**blue arrows**))).

Claims 4 and 17 recite "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose." Adis and Regeneron (8-May-2008) expressly disclose "an 8-week dosing interval." (Ex.1007, 263; Ex.1013, 1; Ex.1002, ¶¶205-08, 228-30, 253-56, 277-80).

Claims 5 and 19 recite "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 VIEW trials continued for at least one year, (Ex.1007, 263 ("after the first year of treatment"); Ex.1013, 1 (same)), which would yield "at least 5 tertiary doses" administered eight weeks apart (Ex.1002, ¶¶209-12, 234-36, 257-59, 285-87).

Claims 6, 7, 18, and 20 recite AMD. Adis and Regeneron (8-May-2008) disclose administering VEGF Trap-Eye/aflibercept for AMD. (Ex.1007, 261, 263-64, 265-66 (Table II), 267-68; Ex.1013, 1; Ex.1002, ¶¶213-15, 231-33, 260-63, 281-84).

Claims 8-10 and 21-23 recite "intraocular administration" and "intravitreal administration." Adis and Regeneron (8-May-2008) disclose VEGF Trap-Eye administered by intravitreal injection. (Ex.1007, 263-264, 265-66 (Table II), 268;

Ex.1013, 1; Ex.1002, ¶¶216-20, 237-41, 264-68, 288-92).

Claims 11, 13, 24, and 26 recite "2 mg" of the VEGF antagonist. Adis and Regeneron (8-May-2008) disclose "2.0 mg." (Ex.1007, 263; Ex.1013, 1; Ex.1002, ¶¶221-23, 242-44, 269-72, 293-96).

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Each anticipatory reference asserted herein (Dixon, Adis, Regeneron (8-May-2008)) is presumed enabling and it is Regeneron's burden to rebut those presumptions. *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 disclosing exact dosage amount and dosing interval was not enabled). Indeed, each reference sets forth a clear method and dosing regimen that POSAs would have no trouble following. Moreover, the preamble—even if it is assumed limiting—does not help. The VEGF Trap-Eye/aflibercept Phase 2 data showed "treating" AMD with VEGF Trap-Eye using even fewer doses, on average, than every-8-week dosing. (Ex.1006, 1576; Ex.1007, 267-68; Ex.1013, 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. Here, inherency is shown by the CLEAR-IT-2 data as well as the VIEW results. (Ex.1018, 2541-45; *id.*, 2537 ("aflibercept is an effective treatment

for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections."). The same analysis applies to PO's anticipated construction of "tertiary dose." (*Supra* § IX(B)).

The claims' "exclusion criteria" are printed matter that are entitled no patentable weight. (*Supra* § IX(C)). Notwithstanding, the exclusion of patients exhibiting the recited exclusion criteria was a necessary, and thus inherent outcome, of the protocol of the VIEW clinical trials disclosed in each of Petitioner's asserted references disclosing the VIEW clinical trials. (Ex.1018, Appendix 2, 3).

B. Obviousness.

The Challenged Claims are also obvious.

1. Legal standard.

Claims are 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, 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 4: The Challenged Claims are obvious over Dixon (either alone or in combination with the '758 patent or the '173 patent).

As discussed above, Dixon discloses each and every element of the Challenged Claims, including the claimed dosing regimen, and thus anticipates them. (*Supra* § XII(A)(2)). Separately, Dixon renders the Challenged Claims obvious in light of the POSA's (i) knowledge of the sequence and domain composition for VEGF Trap-Eye; (ii) clear motivation—as expressly stated in Dixon—to explore less frequent dosing and to apply patient exclusion criteria; and (iii) reasonable expectation of success found in Dixon's disclosure of the positive Phase 2 trial data for VEGF Trap-Eye. (Ex.1002, ¶¶297-308, 332-33).

The Molecule. First, Dixon expressly discloses aflibercept, its domain composition, and informs POSAs that both "aflibercept" and "VEGF Trap-Eye" referred to a single molecule. (Ex.1006, 1573 ("One promising new drug is aflibercept (VEGF Trap-Eye), a fusion protein"), Fig. 1).

Second, Holash (Ex.1004) described the construction of the molecule, and numerous publications, from PO and others, discuss both aflibercept and VEGF Trap-Eye while citing back to Holash and its disclosure of VEGF $Trap_{R1R2}$. (*Supra* § XI(A)). In turn, the '173 patent ties the Holash nomenclature—VEGF $Trap_{R1R2}$—to specific sequences in the '173 patent, and specific nomenclature—VEGFR1R2-FcΔC1(a)—structure, and sequences (the same as those in the '173 patent) in the '758 patent. (Ex.1008, 1:42-52 ("In a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF $trap_{R1R2}$) comprising the nucleotide sequence set forth in SEQ ID NO:1 and the amino acid sequence set forth in SEQ ID NO:2."); Ex.1010, Fig.24A-C, 10:15-17; Ex. 1002, ¶333). As such, a POSA would have understood Dixon's disclosure of VEGF Trap-Eye/aflibercept to refer to the same prior art molecule (*i.e.*, same active agent). (Ex.1006, 1573). Thus, Dixon alone is sufficient, but in any event, the '758 patent and the '173 patent each also set forth the claimed molecule and the amino acid and nucleotide sequences set forth in the Challenged Claims. (Ex. 1002, ¶¶333-34).

Motivation. Prior to January 2011, a known problem existed for which the prior art taught POSAs an obvious solution. *KSR*, 550 U.S. at 419-20. Dixon teaches that monthly intraocular injections presented a "significant" drawback to then-existing AMD therapy. (Ex.1006, 1577 ("Each injection subjects patients to risks"); Ex.1002, ¶¶104-05, 298). First, Dixon discloses motivation to "examine the efficacy

of alternative [less-frequent] dosing schedules." (*Id.*, 1574). Second, Dixon discloses the VIEW, Q8 dosing regimen—*i.e.*, an obvious solution to the need for less frequent than monthly injections.[11] (Ex.1002, ¶¶108, 301). In other words, Dixon "go[es] beyond just illuminating a known problem; [it] also expressly propose[s] the claimed solution." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1375-76 (Fed. Cir. 2013).

Reasonable Expectation of Success. Although no particular level of efficacy is required under the Challenged Claims (IPR2021-00881, Paper 21, 20-23), the CLEAR-IT-2 results disclosed in Dixon (which showed mean improvements of 9.0 letters in BCVA using fewer doses than Q8 dosing) would have provided POSAs a reasonable expectation of success with Q8 dosing. (Ex. 1002, ¶¶300-08).

"Exclusion Criteria." The "exclusion criteria" are not entitled patentable weight. (*Supra* § IX(C)). However, a POSA administering the VIEW1/VIEW2 dosing regimens to AMD patients would have applied the same exclusion criteria: (1) active intraocular inflammation; (2) active ocular or periocular infection; (3) any ocular or periocular infection within the last 2 weeks prior to treatment. (Ex.1002, ¶¶91-93, 97). Indeed, Dixon discloses, *inter alia*, that each intravitreal injection

[11] Dixon discloses Q8 ("8-week") dosing with 2 mg of VEGF Trap-Eye/aflibercept following three monthly doses, (Ex.1006, 1576).

"subjects patients to risks" (Ex.1006, 1577), thus teaching POSAs to avoid administering injections to patients already exhibiting infections or signs of infection. (Ex.1002, ¶¶309-12). A POSA avoiding complications or exacerbating an existing infection by excluding patients with active or recent infections (or signs of infection) from intraocular injections is simply common sense (*i.e.*, eye infections were a known problem associated with intraocular injections). A POSA's common sense solution to a known problem is obvious, not innovative. *KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."). In sum, a POSA reading Dixon would have known to avoid injecting eyes that were infected or showed signs of potential infection.

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For the reasons stated above, Dixon renders the Challenged Claims obvious, either alone or in view of the '758 patent or the '173 patent (which disclose the amino acid and nucleotide sequences for aflibercept known to POSAs).

3. Grounds 5 and 6: The Challenged Claims are obvious over Dixon in combination with Rosenfeld-2006 (Ground 5), or in combination with Heimann-2007 (Ground 6) (and if necessary, in combination with the '758 patent and the '173 patent).

For the reasons presented for Ground 4, Dixon alone renders obvious each of the Challenged Claims. (*Supra* § XII(A)(2)). However, the Challenged Claims also are obvious in view of Dixon in combination with prior art disclosing exclusion of patients from receiving intravitreal injections where those patients have ocular or periocular infections, or signs of such infection (*i.e.*, inflammation)—specifically, Rosenfeld-2006 or Heimann-2007.

"Exclusion Criteria." The recited exclusion criteria are not entitled to patentable weight (*supra* § IX(C)), but are nonetheless disclosed in the prior art.

For example, other major anti-VEGF AMD clinical trials prior to 2011 uses nearly identical exclusion criteria to those in VIEW (and the Challenged Claims). Rosenfeld-2006, which reports the results of MARINA (monthly ranibizumab), discloses a Supplementary Appendix of additional trial information, including several exclusion criteria directed to infection and inflammation:

- "Active intraocular inflammation (grade trace or above)";
- "Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis"; and
- "History of other disease…or clinical laboratory finding giving

> reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk for treatment complications."

(Ex.1058, Appx. 2-3; Ex.1002, ¶¶136, 349).

Given the risks associated with intravitreal injections (as disclosed in Dixon), POSAs would have been motivated to follow Rosenfeld-2006 and exclude patients showing signs of ocular infection or potential infection (*i.e.*, "intraocular inflammation"). (Ex.1002, ¶¶349-50, 352). POSAs also understood that injecting an eye with existing inflammation/infection could confound the physicians' analysis regarding the clinical efficacy of aflibercept. (Ex.1002, ¶¶99-100).

"Active intraocular inflammation." The "active intraocular inflammation" exclusion criteria recited in the Challenged Claims would have been obvious to a POSA, particularly in view of the MARINA exclusion criteria directed to "active intraocular inflammation (grade trace or above) in the study eye" disclosed in Rosenfeld-2006. (Ex.1058, Appx., 2; Ex.1002, ¶349).

"Active ocular or periocular infection." Conjunctivitis, keratitis, scleritis, and endophthalmitis were well known ocular and/or periocular types of infections. (Ex.1002, ¶95; Ex. 1040, 67, 76-77, 85; Ex. 1082, 105; Ex. 1083, 304). Endophthalmitis was a significant concern at the time, having "the greatest

likelihood for acute and irreversible vision loss." (Ex.1057, 678). Accordingly, the "active intraocular or periocular infection" exclusion criteria recited in the Challenged Claims would have been obvious to a POSA, particularly in view of the MARINA exclusion criteria directed to "[i]nfectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye" disclosed in Rosenfeld-2006. (Ex.1058, Appx., 3; Ex.1002, ¶¶349-50).

"Any ocular or periocular infection within the last 2 weeks prior to treatment." A POSA would have known that infections like conjunctivitis can be contagious or infectious for up to two weeks. (Ex.1060, 58 ("[v]iral conjunctivitis is contagious for almost 2 weeks"); Ex.1083, 303 ("symptoms usually are relieved within 2 weeks"); Ex.1002, ¶98).

Further, ocular or periocular infections in the 2 weeks prior to screening would have been understood by a POSA to contraindicate the use of an intravitreally administered agent or affect the interpretation of the results. (Ex.1002, ¶¶99-100, 352). As Dr. Albini explains (*id.*), a recent infection can negatively impact a clinical trial in a number of ways, including (1) increasing the risk of a serious adverse event (e.g., endophthalmitis); (2) influencing baseline measures of visual acuity, retinal thickness, and/or other anatomic assessments; (3) influencing the subsequent post-administration measurements and assessments; and (4) influencing the pharmacokinetics of intravitreally administered drugs (Ex.1057, 680).

In addition, in VIEW, one of the primary aims was to assess non-inferiority to LUCENTIS. (Ex.1006, 1575). Accordingly, POSAs would have been strongly motivated to adopt MARINA exclusion criteria for a clinical trial comparing VEGF Trap-Eye/aflibercept and monthly ranibizumab in order to maintain consistency between the test patient populations, thus enabling better statistical comparison. (Ex.1059, 953; Ex.1002, 351). Indeed, "[a]n equivalence or non-inferiority trial should mirror as closely as possible the methods used in previous superiority trials assessing the effect of the control therapy versus placebo"; "it is important that the inclusion and exclusion criteria, which define the patient population…are the same as in the preceding superiority trials, which have evaluated the reference therapy being used in the comparison." (Ex.1059, 953). In other words, it would have been obvious to use the MARINA eligibility criteria in VIEW. (Ex.1002, ¶¶351-52).

Separately, a POSA would have been motivated to avoid injecting infected or inflamed eyes based on well-known guidelines for intravitreal injections. (*See, e.g.,* Ex.1040, 81 ("[b]acterial infections of the anterior segment and ocular adnexa increase the risk of endophthalmitis and should be treated before performing an intravitreal injection"); *id.*, 85 ("[e]xclude patients with suspected bacterial infections"); *id.*, 67, 76 ("[e]ndophthalmitis is the most feared complication of intravitreal injections" with "potentially devastating consequences"); Ex.1002, ¶¶92-93, 348-50). Given the severe consequences that can arise, it would have been

obvious to exclude patients exhibiting those symptoms prior to the injection. (Ex.1002, ¶¶92-93, 348-50).

Indeed, POSAs would have been generally motivated to reduce the potential of severe side effects from intravitreal injections, and therefore, withholding intravitreal injections from an eye with active infection or inflammation is the essence of *KSR*'s common sense invocation: "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 421.

The Molecule. For the same reasons discussed above in Ground 4 (*supra* § XII(B)(2)), Dixon expressly discloses VEGF Trap-Eye/aflibercept and the amino acid and nucleotide sequences set forth in Challenged Claims 1 and 14, respectively, were either inherent in Dixon or expressly disclosed in the '758 and '173 patents. (Ex. 1002, ¶¶375-76).

Motivation. For the same reasons discussed above in und 4 (*supra* § XII(B)(2)), there was motivation in the art to minimize injections, and adopt dosing regimens that allowed for less frequent intravitreal injections than the FDA-approved monthly dosing for Lucentis. (Ex.1006, 1577; Ex.1002, ¶353). Dixon also

provided an obvious solution to the known "time and financial burden[s] of monthly injections," in its disclosure of the VIEW every-8 dosing regimen (Ex.1006, 1574, 1576); *KSR*, 550 U.S. at 419-20. In other words, Dixon "go[es] beyond just illuminating a known problem; [it] also expressly propose[s] the claimed solution." *Bayer Healthcare*, 713 F.3d at 1375-76.

Reasonable Expectation of Success. A POSA would reasonably expect success administering the VIEW1/VIEW2 dosing regimens to AMD patients in light of the positive Phase 2 CLEAR-IT-2 AMD trial results, also reported in Dixon. A showing of obviousness "does not require absolute predictability of success," *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), but rather a *reasonable* expectation that it would work for its intended purpose, *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 "funnel[s]" the POSA 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), which required (on average) *only 1.6 additional injections* after the four monthly loading doses during the year-long

study. (Ex.1006, 1576; Ex.1002, ¶354). CLEAR-IT-2 confirms the POSA's reasonable expectation of success with the VIEW Q8 regimen.[12] (Ex.1002, ¶354).

For the above reasons, the Challenged Claims are obvious in view of Dixon in combination with Rosenfeld-2006 or Heimann-2007, and if necessary, the '758 and '173 patents. (Ex. 1002, ¶¶347-55, 373-76).

4. No secondary considerations.

Petitioner is not aware of any secondary considerations (or the requisite nexus) that would support a finding of non-obviousness. Even if there were, they are not applicable to the robust anticipation grounds presented in Grounds 1-3, and cannot overcome the strong *prima facie* case of obviousness presented in Grounds 4-6. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

No Unexpected Results. Consistent with the Board's preliminary finding in the -880 and -881 IPRs, the Challenged Claims do not require any particular levels of efficacy. (IPR2021-00881, Paper 21, 21-23, 32). Accordingly, PO's allegation—asserted during prosecution (Ex.1017, 6/25/2018 Remarks, 8-10)—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. Yet, even assuming relevance, PO never informed the Examiner that the dosing regimen it

[12] CLEAR-IT-2 averaged 5.6 injections/year. VIEW averaged 8 injections/year.

claimed demonstrated unexpected results (Ex.1017, 6/25/2018 Remarks, 8-10 (citing *post*-art Heier 2012)) was the subject of numerous *pre*-2011 public disclosures (e.g., Dixon, Adis, and Regeneron press releases). (Ex.1002, ¶¶390-91).

In addition, the CLEAR-IT-2 data showed mean visual acuity gains of nine (9.0) letters and a mean decrease in retinal thickness of 143 μm using a regimen that resulted in fewer average doses (average of 5.6 injections/year) than the VIEW Q8 regimen. (Ex.1006, 1576). Based on the CLEAR-IT-2 results, PO announced that "an 8-week dosing schedule may be feasible." (Ex.1012, 1; Ex.1002, ¶394; Ex.1003, Gerritsen ¶¶46-49, 69-71, 78-80). In addition, there was nothing unexpected about the VIEW Q8 regimens given the general practice of physicians prior to 2011. (Ex.1002, ¶392; Ex.1090, 2 ("I give 3 monthly injections and see them in 8 weeks.")).

No Long-Felt, Unmet Need. PO cannot establish a "need" or show that any such need was "long-felt." PO disclosed the claimed dosing regimen to the general public no later than 2009. Plus, any purported need for the claimed dosing regimen had been fulfilled long before the '681 patent was filed. (Ex.1002, ¶397). Indeed, POSAs had been implementing such regimens well before the priority date. (Ex.1090, 1-2 ("I give 3 monthly injections and see them in 8 weeks"); Ex.1022, 149:15-17 ("But our clinical practice, as was stated in the 2007 paper, was to give three monthly doses, and then assess [in 8 weeks] how the patient is doing.")).

No Nexus. PO cannot establish a nexus of any purported commercial success to the Challenged Claims. (Ex.1002, ¶398). PO's proofs in related IPRs were deficient for a host of reasons, including, but not limited to, failure to tie the claimed regimen to any substantial real-world physician use, failure to consider blocking patents and blocking regulatory exclusivity covering EYLEA®, failure to account for the massive marketing spend around EYLEA®, and failure to account for the accused illegal kickback schemes around Regeneron's EYLEA® rebate and discount programs. (*See, e.g.*, IPR2021-00881, Paper 62, 35-37). Petitioner reserves the right to more specifically respond to any assertions of secondary considerations that Regeneron alleges during this proceeding.

XIII. CONCLUSION.

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

Dated: July 1, 2022

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. 10,130,681 B2 and Exhibits 1001-1094 were served on July 1, 2022, via FedEx Priority Overnight on the Patent Owner at the correspondence address of record for U.S. Patent No. 10,130,681 B2 as evidenced in Public Pair:

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201 Redwood Shores Parkway
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Redwood City, CA 94065

Regeneron Pharmaceuticals, Inc.
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Patent Department
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 13,821 words. This total does not include the tables of contents and authorities, mandatory notices, the caption page, table of exhibits, certificate of service, or this certificate of word count. 37 C.F.R. § 42.24(a).

Dated: July 1, 2022

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