UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00566

U.S. Patent No. 10,888,601

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,888,601

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1003	Expert Declaration of Mary Gerritsen, Ph.D. in Support of Petition for Inter Partes Review of U.S. Patent No. 10,888,601 B2, dated June 30, 2022 ("Gerritsen"), filed in IPR2022-01226
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1005	Quan Dong Nguyen et al., A Phase I Study of Intravitreal Vascular Endothelial Growth Factor Trap-Eye in Patients with Neovascular Age-Related Macular Degeneration, 116 OPHTHALMOLOGY 2141 (2009) ("Nguyen-2009")
1006	James A Dixon et al., VEGF Trap-Eye for the Treatment of Neovascular Age-Related Macular Degeneration, 18 EXPERT OPINION ON INVESTIGATIONAL DRUGS 1573 (2009) ("Dixon")
1007	Adis R&D Profile, Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye, 9 DRUGS R&D 261 (2008) ("Adis")
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1009	U.S. Patent No. 7,396,664 B2 ("'664 patent")
1010	U.S. Patent No. 7,374,758 B2 ("'758 patent")
1011	F Semeraro et al., Aflibercept in Wet AMD: Specific Role and Optimal Use, 7 DRUG DESIGN, DEV. & THERAPY 711 (2013) ("Semeraro")
1012	Press Release, Regeneron, Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration (Apr. 28, 2008), http://investor.regeneron.com/releasedetail.cfm?releaseid=394066 ("Regeneron (28-April-2008)")
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1092	Amino acid sequence alignment of SEQ ID NO:2 of the '681 and '601 patents with SEQ ID NO:16 of the '758 patent and SEQ ID NO:2 of the '173 patent ("AA Alignment vs 758 and 173 patents")
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1094	ClinicalTrials.gov, 1997: Congress Passes Law (FDAMA) Requiring Trial Registration, U.S. NAT'L LIBRARY MED. (Oct. 2020), https://clinicaltrials.gov/ct2/about-site/history ("History-ClinicalTrials.gov")
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1099	*Mylan Pharmaceuticals, Inc. v. Regeneron Pharmaceuticals, Inc.* PTAB-IPR2022-01226, Mylan's Petition, Paper 2.
1100	*Mylan Pharmaceuticals, Inc. v. Regeneron Pharmaceuticals, Inc.* PTAB-IPR2022-01226, Institution Decision, Paper 22.
1101	*Mylan Pharmaceuticals Inc. v. Regeneron Pharmaceuticals, Inc.* PTAB-IPR2021-00881, Final Written Decision, Paper 94.

Samsung Bioepis Co., Ltd. ("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 1-9, 34-39, 41-43, and 45 (the "Challenged Claims") of U.S. Patent No. 10,888,601 ("'601 patent") (Ex.1001), assigned to Patent Owner, Regeneron Pharmaceuticals, Inc. ("Regeneron" or "PO").

This Petition replicates Mylan's petition filed in IPR2022-01226 (the "Mylan IPR"), with the exception of the petitioner-specific mandatory notices, and asserts the same grounds of unpatentability of the '601 patent upon which the Patent Trial and Appeal Board (the "Board") has already instituted review in the Mylan IPR. Accordingly, there exists a reasonable likelihood that Petitioner will prevail in demonstrating unpatentability of at least one of the Challenged Claims, and Petitioner respectfully seeks to join the Mylan IPR.

This Petition is timely and proper under 35 U.S.C. § 315(c).

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 published and known to persons of ordinary skill in the art (hereafter, "POSAs") before 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 regimens to POSAs as early as 2008. The dependent claims drawn to visual acuity measures and exclusion criteria either fail to carry patentable weight or are inherent and obvious variations on the subject matter of the independent claims. Accordingly, the Challenged Claims are unpatentable.

Petitioner thus files this Petition, supported by expert declarations from Dr. Thomas Albini—a renowned ophthalmologist (Ex.1002), and Dr. Mary Gerritsen—a pharmacologist with over thirty years' experience (Ex.1003). Solely to preserve its right to rely on expert testimony in the event that joinder is not granted or in the case that the Mylan IPR is settled, Petitioner further relies on the accompanying Declaration of Benjamin H. Bloom, M.D. (Ex.1097), in which Dr. Bloom adopts the opinions set forth by Drs. Albini and Gerritsen in connection with the Mylan IPR.

Anticipation & Obviousness. Each Challenged Claim is anticipated. VEGF Trap-Eye (aflibercept) and its domain components were known and disclosed in the prior art, including in each of Petitioner's asserted references. (*See* Ex.1006, 1576 (Fig. 1); Ex.1008; Ex.1010).

Petitioner's references disclosing Regeneron's Phase 3 VIEW AMD trials describe all dosing steps of the Challenged Claims—including administering three monthly loading doses of VEGF Trap-Eye/aflibercept, followed by every-8-week

dosing. The recited visual acuity measures are unpatentable given that the prior art discloses administration of the same compound according to the same dosing schedule set forth in the claims, and though the recited exclusion criteria are not entitled to patentable weight, they are nonetheless inherent.

The claimed methods also are obvious in view of the risks and financial burden of monthly intravitreal injections—the approved AMD dosing regimen for the existing anti-VEGF therapy prior to EYLEA's approval, LUCENTIS® (ranibizumab). (Ex.1006, 1574). POSAs were motivated to pursue less frequent dosing schedules, like the VIEW Phase 3 clinical trial every-8-week dosing Regeneron itself (among others) placed into the public domain. Combined with the abundance of positive, prior art data from Regeneron's other clinical trials, a POSA would have reasonably expected success administering the claimed dosing regimens. The recited visual acuity measures do not save the dependent claims from obviousness given that Regeneron's aflibercept molecule already had "Phase I and II trial data indicating safety, tolerability and efficacy for the treatment of neovascular AMD." (Ex.1006, 1573).

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

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

The real party-in-interest ("RPI") for Petitioner is Samsung Bioepis Co., Ltd.

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

Mylan filed a petition requesting *inter partes* review of the Challenged Claims on July 1, 2022 ("Mylan's IPR Petition"). *See* IPR2022-01225, Ex.1099, Paper 2. On January 11, 2023, the Board instituted *inter partes* review of the Challenged Claims based on the grounds identified in Mylan's petition. *Id.*, Ex.1100, Paper 22.

The '601 patent is in the same family as U.S. Patent Nos. 9,254,338 ("'338 patent") and 9,669,069 ("'069 patent"). In May 2021, Mylan Pharmaceuticals Inc. filed petitions requesting for *inter partes* review of those two patents. *See* IPR2021-00881 ("'338 IPR") and IPR2021-00880 ("'069 IPR"). The Board instituted review for the '338 and '069 patents and found all challenged claims of those patents unpatentable in Final Written Decisions issued on November 9, 2022. *See* '338 IPR, Ex.1101, Paper 94; '069 IPR, Paper 89.

The '601 patent is also in the same family as U.S. Patent No. 10,130,681 ("'681 patent"). Mylan filed a petition requesting IPR of the '681 patent on July 1, 2022 (IPR2022-01225) ("Mylan '681 IPR"). The Board instituted *inter partes* review of the '681 patent on January 11, 2023. *See,* Mylan '681 IPR, Paper 21. Petitioner filed an *inter partes* review petition against the '681 patent on January 6, 2023. *See* IPR2023-00442 ("Petitioner's 681 IPR"). The Board has not yet issued its institution decision in Petitioner's '681 IPR.

To the best of Petitioner's knowledge, the following are judicial or administrative matters that potentially would affect, or be affected by, a decision in this proceeding: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, NDWV-1-22-cv-00061, *United States v. Regeneron Pharms., Inc.*, No. 1:20-cv-11217-FDS (D. Mass.).

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)-(4))

Petitioner hereby identifies its lead and backup counsel as follows:

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Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed herewith.

D. Service Information (37 C.F.R. § 42.8(b)(4))

Please send all correspondence to the lead and backup counsel at the addresses shown above. Petitioner consents to service by e-mail at the addresses of lead and back-up counsel shown above.

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 505708.

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

Petitioner certifies that the '601 patent—which issued on November 20, 2018—is available for IPR and that Petitioner is not barred or estopped from requesting an IPR challenging any claim thereof on the grounds identified herein. Neither Petitioner nor any other RPI has filed a civil action challenging the validity, or been served with a complaint alleging infringement, of the '601 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 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 '601 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), (b) and (d).** Petitioner submits that neither "the same [nor] substantially the same" art or arguments were previously presented to the Office during prosecution of the Challenged Claims. First, none of Petitioner's grounds rely on prior art actually applied against the claims during prosecution, nor discussed by the Examiner. Instead of the VIEW dosing regimen prior art Petitioner asserts here under §§102 and 103, the Examiner only rejected the claims for obviousness-type double patenting ("OTDP") during prosecution. (Ex.1017, 796-803).

Second, the only fact PO can point to is that Petitioner's asserted references were included among hundreds of references in a series of IDS submissions. 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)); *see also Amazon.com, Inc. v. M2M Sols. LLC*, IPR2019-01205, 2020 WL 448385, at *7 (P.T.A.B. Jan. 27, 2020) (instituting IPR where "the prosecution history record shows that the various IDSs include at least about a few hundred references" and "[n]othing in the record indicate[d] that the Examiner substantively considered…the prior art"); *id.* at *7 ("[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." (citations omitted)); *Shenzhen Zhiyi Tech. Co. v. iRobot Corp.*, IPR2017-02137, Paper 9, 9-10 (P.T.A.B. Apr. 2, 2018) (declining to deny institution under §325(d) when reference merely cited in an IDS; reference not relied upon by the Examiner, but rather, was merely "included in the approximately fifteen pages of cited references"); *Nitto Denko Corp. v. Hutchinson Tech. Inc.*, IPR2018-00955, Paper 7, 15-17 (P.T.A.B. Dec. 4, 2018) (instituting IPR review despite asserted reference being submitted in an IDS which the examiner initialed). Indeed, PO's serial IDS submissions of Petitioner's asserted art buried among hundreds of other references does not rise to the level of candor and good faith required before the Patent Office.

In short, Petitioner's asserted prior art references were neither "involved" nor "evaluated" during prosecution, and therefore, the art and arguments provided herein are neither the same nor substantially the same as those previously considered by the Office.[1] *Becton, Dickinson*, IPR2017-01586, Paper 8, 17; 35 U.S.C. §325(d).

***Becton, Dickinson* Factors (c), (e), (f): The Examiner Erred.** As explained above, the intrinsic record does not reflect that Petitioner's grounds were presented to, or considered by, the Examiner. Nonetheless, to the extent the Board disagrees and determines *Becton Dickinson* factors (a), (b), and (d) are satisfied, discretionary denial still is unwarranted because the Examiner overlooked each reference's anticipatory disclosures, constituting material error, relying instead on a single round of OTDP rejections over patents in the same family.[2] *See Advanced Bionics*, 2020

[1] Should PO point to its 2018 and 2019 IDS submissions including Dixon and a corresponding claim chart during prosecution of the related '345 patent, that disclosure is only directed to quarterly and PRN dosing claims—not the 8-week dosing—and thus is irrelevant to the Challenged Claims.

[2] Indeed, the Examiner assigned to this family has fallen into a pattern of only asserting OTDP rejections against most pending claims, consistently ignoring relevant art and the claims' significant § 112 issues, leading Regeneron to obtain a

WL 740292, at *4 (listing silence as evidence of error). As shown below, multiple prior art references disclose the VIEW 8-week dosing regimen and clearly anticipate the issued claims; the only plausible explanation for the Examiner not rejecting the claims based on those disclosures is failure to have seen, appreciated or understood the disclosures.

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; Ex.1097) that set forth the POSA's understanding of the prior art disclosures, including, *inter alia*, the dependent claims' best corrected visual acuity ("BCVA") limitations, and the additional art and asserted combinations relevant to the exclusion criteria. *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.*

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thicket of dosing regimen patents. No fewer than seven (7) patents already have issued from this family, and five (5) applications remain pending.

Interface, Inc., IPR2013–00333, 2013 WL 8595289, at *2 (P.T.A.B. Dec. 9, 2013) (same).

In sum, Petitioner presents challenges never applied or considered by the Examiner during prosecution of the '601 patent claims, and the Examiner's failure to reject claims over the art and grounds herein constitutes material error.

VII. OVERVIEW OF PETITIONER'S CHALLENGES AND REQUESTED RELIEF

A. Statutory Grounds of Challenge

The following prior art references anticipate the Challenged Claims:

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

In addition, the following render the Challenged Claims obvious:

Ground	Proposed Rejections Under 35 U.S.C. § 103
5	Dixon alone or in view of the ’758 or ’173 patents
6	Dixon in combination with Rosenfeld-2006 (and if necessary, the ’758 or ’173 patents) (claims 9 and 36)
7	Dixon in combination with Heimann-2007 (and if necessary, the ’758 or ’173 patents) (claims 9 and 36)

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

VIII. OVERVIEW OF THE ’601 PATENT[3]

The ’601 patent confirms that 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, but reserves all rights to challenge said priority date. The ’601 patent is subject to the AIA given the inclusion of new matter in Application No. 13/940,370, filed July 12, 2013.

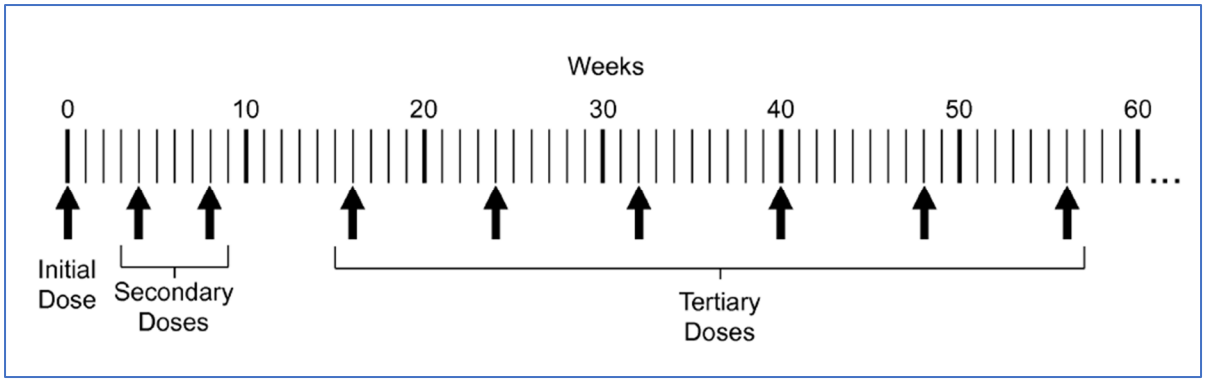
("VEGF")[4] inhibition. (Ex.1001, 1:31-60). Indeed, prior to 2011, ranibizumab (LUCENTIS®), an anti-VEGF antibody fragment marketed by Genentech, was FDA-approved for monthly administration via intravitreal injection to treat AMD. (*Id*., 1:57-60; *see also* Ex.1048, 1). Despite being approved for monthly dosing, ranibizumab was often administered on a PRN (i.e., pro re nata, or "as needed") basis, and Genentech's clinical trials were testing extended dosing regimens, and showing that PRN dosing could achieve similar outcomes to monthly dosing, using fewer injections. (Ex.1030, 6-7; Ex.1002, ¶¶72-74; Ex.1097). Bevacizumab (AVASTIN®), an anti-VEGF antibody, was not approved for ocular indications, but was extensively used off-label to treat angiogenic eye disorders. (Ex.1006, 1574; Ex.1002, ¶64; Ex.1097). Because there was no approved dosing regimen for bevacizumab in treating eye disorders, it too was often administered PRN. (Ex.1025, 1369; Ex.1047, 8; Ex.1049, 24-25; Ex.1002, ¶73; Ex.1097). In other words, extended dosing regimens were already in use prior to 2011. Yet the '601 patent

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

purports a need in the art for regimens that allow less frequent dosing. (Ex.1001, 1:64-67).

The '601 patent broadly claims the prior art VIEW1/VIEW2 regimen, which became the FDA-approved regimen for EYLEA® (i.e., VEGF Trap-Eye/aflibercept). (*See*, e.g., Ex.1001, 21:41-46 (Claim 1)). Dependent claims include efficacy criteria wherein the subject of the claimed method loses less than, or gains at least, fifteen letters of Best Corrected Visual Acuity (BCVA) score. (See, e.g., *id*., 21:49-51 (Claim 3); *id*., 21:55-56 (Claim 5)). The '601 patent claims also include variations of two of the thirty-seven exclusion criteria for the prior art VIEW1/VIEW2 trials: "18. Active intraocular inflammation in either eye. 19. Active ocular or periocular infection in either eye," while omitting the other thirty-five exclusion criteria. (*Id*., 11:44-45; *id*., 21:65-67 (Claim 9); *id.*, 24:22-24 (Claim 36); *see id*., 10:64 – 12:22). The exclusion criteria are mentioned only once in the specification, in Example 4, describing the Phase 3 AMD VIEW trials. (See *id*., 9:21 – 14:4).

This VIEW1/VIEW2 dosing regimen is described as "an exemplary dosing regimen of the present invention" and is depicted graphically by the Figure of the '601 patent:



(*Id*., 2:55-62, Fig.1; *see also id*., 4:10-12). The Figure illustrates and exemplifies a dosing regimen falling within the Challenged Claims.

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

Under 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).

A. "A METHOD FOR TREATING AN ANGIOGENIC EYE DISORDER IN A PATIENT IN NEED THEREOF" AND "A METHOD FOR TREATING AGE RELATED MACULAR DEGENERATION."

1. The "method for treating" preamble is non-limiting, and does not require construction.

The "method for treating" preambles of independent claims 1 and 34 are each "merely a statement of purpose or intended use" for the claimed dosing regimen(s) and are 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" provides neither antecedent basis for any other claim element, nor life, meaning, or vitality to the claimed regimen. *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 was non-limiting where it "does not change the express dosing amount or method already disclosed in the claims, or otherwise result in a manipulative difference in the steps of the claims"). There also is no evidence that Regeneron asserted the "method for treating" preamble to traverse Examiner rejections.

Moreover, Regeneron's reliance on alleged "unexpected results" during prosecution of related patents does not render the preamble a necessary feature of the claims. *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 5753968, *5 (P.T.A.B. Sept. 22, 2016) ("method of treating a patient" preamble 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. Regeneron's argument that the "method for treating" preamble is a positive limitation should be rejected.

In related proceedings, Regeneron has asserted that analogous "method for treating" preambles in related patents are positive claim limitations and has provided a moving target of proposed constructions for the 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);
- "Regeneron does not advance claim construction positions for these terms," (IPR2021-00880, Paper 10, 19).

It remains to be seen which of these approaches Regeneron will advance here, or if they will submit yet another proposal. Regardless, any attempt to read efficacy limitations into the preamble should be rejected. First, the preamble 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 a statement of *intended* purpose, and not a limitation. *Bristol-Myers*, 246 F.3d at 1375; *Copaxone*, 906 F.3d at 1022-23.

Second, "method for treating" provides no antecedent basis for any other claim element. 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. Consequently, the preamble is non-limiting.

Third, even if the Board finds the preamble limiting, the independent claims are not *required* to have any particular degree of efficacy. IPR2021-00881, Paper 21, 20, 32. Indeed, Regeneron's efforts to avoid explaining what exactly "high level of efficacy that is not inferior to the existing standard-of-care" means in the related '338 patent IPR speaks volumes about the degree of ambiguity its proposed construction injects into the claims. Consequently, to the extent the preamble is limiting, it is "a statement of the intentional purpose for which the

method must be performed." *GlaxoSmithKline LLC v. Glenmark Pharms., Inc.*, No. 14-877-LPS-CJB, 2016 WL 3186657, at *7 (D. Del. June 3, 2016).

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

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

To the extent the Board determines it to be limiting, the preamble phrases should be construed to have their plain and ordinary meaning, "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). As the '601 patent shares the same specification as the '338 patent, Regeneron's arguments as to any degree of claimed effectiveness for independent claims 1 and 34 similarly fail, and the phrase "a method for treating an angiogenic eye disorder in a patient" has the same meaning and does "not require

the recited method steps to provide an *effective* treatment." *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.").

To the extent PO presents the same arguments here that it presented in the 881 IPR, they should be rejected.

First, PO's anticipated proposed construction lacks support in the intrinsic record.[5] Thus, 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

[5] There are no data presented in the '601 patent setting forth the non-inferiority of the claimed regimen compared to monthly ranibizumab for at least "diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization," (*see, e.g.*, claim 42), or any of the other angiogenic eye disorders listed in the patent, (Ex.1001, 5:21-39). Even for AMD, which PO relies on in the '338 IPR, PO admits that a significant proportion of AMD patients were excluded from the VIEW study (IPR2021-00881, Paper 41, 43-46), meaning no non-inferiority data exist for those patients.

can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist"—not "must be" achieved. (Ex.1001, 2:11-13 (emphasis added); IPR2021-00881, Paper 21, 21). The specification states "[a]n example of a dosing regimen of the present invention is shown in FIG. 1," (Ex.1001, 2:23-24), focusing on temporal dose sequence, not efficacy outcomes.

Second, under PO's anticipated construction, a POSA is only able to determine infringement (or not) *retroactively*. A POSA, treating a patient, can only determine whether or not that treatment infringed *after-the-fact* by exhibiting a "high level of efficacy that is not inferior to the existing standard-of-care."[6] (IPR2021-00881, Paper 41, 12). A construction that so undermines the notice function of patent claims cannot be correct. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003) (rejecting proposed construction where "a given embodiment would simultaneously infringe and not infringe the claims," depending on the circumstances); *see also Takeda Pharm. Co. v. Zydus Pharms.*

[6] Non-inferiority is a population-based clinical trial statistical determination. There is no support in the '601 patent specification describing how to assess whether the treatment of the claimed *single patient* is "not inferior to the existing standard of care."

USA, Inc., 743 F.3d 1359, 1365 (Fed. Cir. 2014); *Oakley, Inc. v. Sunglass Hut Int'l*, 316 F.3d 1331, 1341-43 (Fed. Cir. 2003).

Third, PO's anticipated "high level of efficacy" construction generates §112 enablement, written description, and indefiniteness problems, because the specification provides no means or parameters for ascertaining what constitutes a "***high*** level of efficacy." (Ex.1002, ¶¶48-52; Ex.1097); *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 the angiogenic eye disorder that is being treated and may further vary with respect to time, patient, and treating physician. Accordingly, PO's imported limitation opens the claims to a near-infinite level of variability and subjectivity. A claim construction that constitutes such a moving target cannot be correct.

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

Independent claim 34 recites the phrases "initial dose," "secondary dose," and "tertiary dose." A POSA would understand each as expressly defined in the '601 patent specification. (Ex.1001, 3:42-49; Ex.1002, ¶44-45; Ex.1097). 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, 3:62-67; Ex.1002, ¶44-45; Ex.1097). 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 context of the related '338 patent, 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). As the '601 patent shares the same specification as the '338 patent, Regeneron's prior arguments, if presented here, similarly fail, and "tertiary dose(s)" means "the dose(s) which are administered after the secondary dose(s)." *See Samsung Elecs.*, 925 F.3d at 1378.

C. "WHEREIN EXCLUSION CRITERIA FOR THE PATIENT INCLUDE."

Dependent claims 9 and 36 recite two exclusion criteria. (Ex.1001, 21:65-67 (Claim 9), *id.*, 24:22-24 (Claim 36)). The exclusion criteria are entitled to no patentable weight, and thus should not be treated as claim limitations.

1. The Claimed Exclusion Criteria Are Entitled No Patentable Weight Under the Printed Matter Doctrine.

Determination of whether a claim limitation is entitled to patentable weight under the printed matter doctrine is a two-step process, the first of which "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. Prod. IP Ltd.*, 890 F.3d 1024, 1032 (Fed. Cir. 2018) (quoting *DiStefano*, 808 F.3d at 848). The second step "is to ascertain whether the printed matter is functionally related to" the rest of the claim. *Id*.

In *Praxair*, 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 preexisting left ventricular dysfunction." 890 F.3d at 1029. The limitation constitutes a mental step (deciding not to treat the patient) on the basis of information (a preexisting condition). *Id.* at 1033.

In the '601 patent, the "exclusion criteria" should similarly be considered "printed matter" carrying "no patentable weight" because they constitute informational content that lacks a functional relationship to the other claim elements. First, the claimed exclusion criteria are mere information (preexisting conditions). The "electing" step in *Praxair* was insufficient to impart patentability to those mental step/printed material claims, *and the claims here do not even have that*—no

active step of applying the exclusion criteria, or assessing the patient is set forth in the claims. Even assuming that an applying step could be inferred, it is a mental step.

Second, the claims do not dictate that any step be taken or alteration be made to the regimen in response to the exclusion criteria—there is no functional relationship between the specific information at issue (preexisting conditions) and the other claim elements (physical treatment steps of administering a VEGF antagonist). Thus, the exclusion criteria are "mental steps" that "attempt to capture informational content," and lack a functional relationship to the claimed treatment method, and should be "considered printed matter lacking patentable weight." *Praxair*, 890 F.3d at 1033.

Further, application of the printed matter doctrine as a matter of claim construction is proper. *See id.* The analysis is an effort to define the scope and meaning of specific claim terms, and whether the exclusion criteria aspect/element "will not distinguish the invention from the prior art in terms of patentability" under anticipation and obviousness analyses. *In re Gulack*, 703 F.2d 1381, 1385 (Fed. Cir. 1983); *see also Praxair*, 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."). Accordingly, this "only require[s] analyzing and interpreting the meaning of the claim language. That is claim

construction, which is ultimately a legal inquiry." *Praxair*, 890 F.3d at 1033 (citation omitted).

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; Ex.1097; *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 SCOPE AND CONTENT OF THE PRIOR ART

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

A. VEGF TRAP-EYE/AFLIBERCEPT BACKGROUND

Aflibercept is an engineered prior art fusion protein consisting of domain 2 of the human VEGF receptor 1 (VEGFR1); domain 3 of the human VEGF receptor 2 (VEGFR2); fused to the Fc portion of human IgG_1. (*See* Ex.1004, 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; Ex.1097).

These prior art disclosures are consistent with Regeneron's later confirmatory statements to the Patent Office that (1) aflibercept and VEGF Trap-Eye were synonymous; (2) the construction of VEGF Trap-Eye/aflibercept was described in Holash 2002; and (3) the sequence and domain composition of VEGF Trap-Eye/aflibercept was set forth in Regeneron's prior art '758 and '959 patents. (Ex.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…[t]hus aflibercept is a fusion protein encoded by a nucleic acid sequence of SEQ ID NO: 15."; "aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP$_{R1R2}$")). Regeneron also represented to the Patent Office during prosecution of related patents that the VIEW clinical trials correspond to Example 4 in the specification—in other words, the same trials, and the same molecule, disclosed in Petitioner's art (*e.g.*, Dixon, etc.) and later claimed in the '601 patent. (*See, e.g.*, Ex.1096, 177 (6/25/2018 Remarks)).

Numerous prior art publications discussing both aflibercept and VEGF Trap-Eye cite back to Holash's disclosure of VEGF-Trap$_{R1R2}$. (Ex.1026, 18363, 18370 ("aflibercept" included as a keyword, citing back to Holash (ref. 20)); Ex.1028, 2 (discussing VEGF Trap-Eye and 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)," citing Holash);

Ex.1031, 1009-10 (discussing VEGF Trap-Eye and its structure, and citing back to Holash); Ex.1036, 4414, 4420 (citing to Holash for the following statement: "To block VEGF, we employed the VEGF Trap (aflibercept)...")).

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 (emphasis added)). 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.1087). 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; Ex.1097).

B. ANTI-VEGF THERAPY

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.

Ranibizumab (LUCENTIS®) was approved for monthly dosing but was often being used on a PRN basis, given the risks, cost, and inconvenience of monthly dosing. Bevacizumab (AVASTIN®) was approved for cancer indications but being used off-label to treat AMD. At the time, ranibizumab approved indications, and the bevacizumab off-label use, overlapped those Regeneron was exploring for EYLEA®. Both ranibizumab and bevacizumab, like aflibercept, are VEGF antagonists.

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 '601 patent.

C. EXCLUSION CRITERIA

Historically, certain patient populations, such as those with pre-existing conditions, were excluded from anti-VEGF therapy treatment. For example,

Genentech's LUCENTIS (ranibizumab) clinical trials employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study 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, 140-41; Ex.1097; *compare with* Ex.1001, Claim 9). It was also common practice to delay intravitreal injections in patients exhibiting increased risk for infection or inflammation. (*See* Ex.1040, 76 (advising 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 (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"), 85 ("[e]xclude patients with suspected bacterial infections or the anterior segment (e.g., blepharitis, conjunctivitis)"); *see also* Ex.1006, 1577 ("Each injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis"); Ex.1002, ¶93; Ex.1097).

D. PETITIONER'S PRIOR ART REFERENCES

1. Dixon (Ex.1006).

Dixon was published in 2009 and thus constitutes prior art under 35 U.S.C. § 102. 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's disclosures are described in detail in the expert declaration of Dr. Albini. (Ex.1002, ¶¶101-11; Ex.1097).

Dixon discloses that for AMD treatments, "***[o]ne*** promising new drug is aflibercept (VEGF Trap-Eye), ***a*** fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2," and that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (Ex.1006, 1573, 1575). Accordingly, a POSA would have understood that the active ingredient was the same in both presentations. (Ex.1002, ¶¶102-03; Ex.1097). For example, in addition to Dixon's description of VEGF Trap-Eye/aflibercept as "***one*** promising new drug," 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.")).

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 notes the "time and financial burden of monthly injections" led researchers "to examine the efficacy of alternative dosing schedules." (*Id.*, 1574).

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

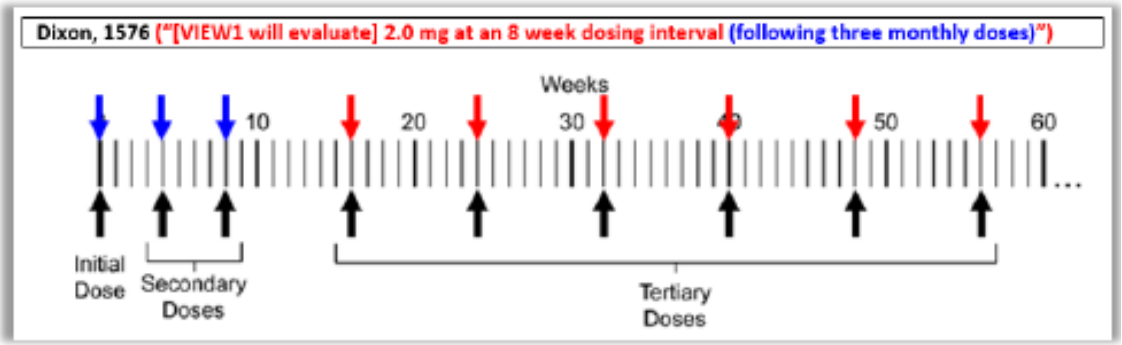


Figure 1. (Modified from Fig. 1 of the '601 patent).

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**). (Ex.1006, 1576; Ex.1002, ¶¶108, 150; Ex.1097). 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) EDTRS letters and a mean decrease in retinal thickness of 143 μm. (Ex.1006, 1576; Ex.1002, ¶¶106-07; Ex.1097). 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, 306, 351; Ex.1097).

In addition, Dixon discloses that VIEW was to be a non-inferiority study that included comparison with monthly ranibizumab, (Ex.1006, 1575), and that "[e]ach injection subjects patients to risks of cataract, intraocular inflammation, retinal detachment and endophthalmitis," (*id.*, 1577).

2. Adis (Ex.1007)

Adis was published in 2008 and thus constitutes prior art under 35 U.S.C. § 102. 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), and that "***[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." (*Id.* (emphasis added); Ex.1002, ¶113; Ex.1097).

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, 189; Ex.1097) (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, ¶¶115, 118; Ex.1097).

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; Ex.1097). 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. PO has not contested Ex.1013's status as prior art in related proceeding IPR2021-00881.

Regeneron (8-May-2008) reports VIEW1/VIEW2 Phase 3 AMD trials and sets forth the dosing regimen encompassed by the Challenged Claims: "In the first year, the VIEW2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at . . . 2.0 mg at an 8-week dosing interval, ***including one additional 2.0 mg dose at week four*** [i.e., doses at weeks **0, 4, 8, 16, 24, 32, 40, and 48**]." (Ex.1013, 1 (emphasis added); Ex.1002, ¶120; Ex.1003, ¶¶44-55, 76-78; Ex.1097).

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, ¶122; Ex.1097).

4. NCT-795 (Ex.1014).

NCT-795 is an on-line record disclosing the VIEW1 regimen Regeneron submitted to the ClinicalTrials.gov database maintained by the National Library of Medicine at the National Institutes of Health ("NIH"). ClinicalTrials.gov is a website "***intended for a wide audience***, including individuals with serious or life-threatening diseases or conditions, ***members of the public***, ***health care providers, and researchers***." (*See* Ex.1094, 2 (emphasis added); Ex.1003, ¶¶79-90; Ex.1097).

NCT-795 is a § 102 printed publication. *Hulu, LLC v. Sound View Innovations*, No. IPR2018-01039, 2019 WL 7000067, *5 (P.T.A.B. Dec. 20, 2019). The Board has found a ClinicalTrials.gov printout analogous to NCT-795 qualifies as a prior art printed publication. *Grünenthal GMBH v. Antecip Bioventures II LLC*, No. PGR2019-00026, 2020 WL 4341822, *8 (P.T.A.B. May 5, 2020).

Here, the evidence confirms that NCT-795—including the VIEW1 dosing regimen and other clinical study details provided therein—was publicly available on the ClinicalTrials.gov website prior to January 13, 2011. ***First***, the History of Changes archive that ClinicalTrials.gov maintains demonstrates the VIEW1 regimen was disclosed to the public before 2011. (Ex.1014, 8). ***Second***, Wayback Machine

records and the corresponding affidavit provided herein (Ex.1095, 1-2, 8-11) show NCT-795's public availability prior to 2011. *Sandoz Inc. v. Abbvie Biotechnology Ltd.*, No. IPR2018-00156, 2018 WL 2735468, *4-5 (P.T.A.B. June 5, 2018). ***Third***, NCT-795 was expressly cited in the prior art itself (*see, e.g.*, Ex.1006, 1579 (Bibliography No. 46) ("Accessed 28 Sep 2008"); Ex.1072, 94-95), demonstrating its actual publication and availability to interested, POSAs. (Ex.1003, ¶¶79-90; Ex.1002, ¶129; Ex.1097).

In support of this Petition, Dr. Gerritsen provides her expert opinion that clinical study details were publicly accessible from ClinicalTrials.gov to POSAs as of their posted dates. (Ex.1003, ¶¶79-80; Ex.1097; *see also* Ex.1002, ¶¶124-29). As such, NCT-795 is a printed publication that was accessible to the public more than one year before January 13, 2011 and thus constitutes prior art under 35 U.S.C. § 102. In related proceedings, PO has not contested the public availability or prior art status of NCT-795.

NCT-795 discloses Regeneron's Phase 3 VIEW1 trial. (Ex.1014, 3-5). Specifically, NCT-795 discloses the treatment arms of the VIEW1 study, including the every-8-week treatment regimen: "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (Ex.1014, 4-5, 8; Ex.1002, ¶¶100-03; Ex.1097) (i.e., doses at weeks **0, 4, 8, 16, 24, 32, 40, 48**, etc.).

NCT-795 also discloses the primary outcome measure of the VIEW 1 trial: "[t]he proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline." (Ex.1014, 9). NCT-795 also discloses a number of secondary outcome measures, including: "[t]he proportion of subjects who gain at least 15 letters of vision at Week 52." (Ex.1014, 9).

5. '758 patent (Ex.1010)

The '758 patent issued on May 20, 2008, and thus constitutes prior art under 35 U.S.C. § 102.

The '758 patent, assigned to Regeneron, discloses "[m]odified chimeric polypeptides with improved pharmacokinetics," including, 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; *see also* Ex.1024, 2, 6-7; Ex.1002, ¶135; Ex.1097; 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; *see also id.*, 3:5-29; Ex.1002, ¶135; Ex.1097).

6. ’173 patent (Ex.1008)

The ’173 patent issued May 12, 2009, and published April 10, 2008, and thus is prior art under 35 U.S.C. § 102.

The ’173 patent teaches methods of reducing angiogenesis through the administration of the VEGF antagonist fusion protein claimed in the ’601 patent. (Ex.1008, 1:32-56, SEQ ID NOS:1 and 2; Ex.1092; Ex.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).

7. Rosenfeld-2006 (Ex.1058).

Rosenfeld-2006 was published in 2006, and thus is prior art under 35 U.S.C. § 102.

Rosenfeld-2006 sets forth the results of the ranibizumab Phase 3 clinical trial, MARINA, assessing monthly dosing of ranibizumab compared to sham (placebo) injections. Rosenfeld-2006 reports that ranibizumab is “a recombinant, humanized monoclonal antibody Fab that neutralizes all active forms of VEGF-A.” (Ex.1058, 1420). Rosenfeld-2006 discloses the results of the MARINA ranibizumab study. (Ex.1058, 1425-27).

Rosenfeld-2006 further discloses that eligibility criteria were provided in Table 1 of the Supplementary Appendix, available with the full text at www.nejm.org. (Ex.1058, 1420-21). Table 1 provides a full list of exclusion criteria, including the following:

- Active intraocular inflammation (grade trace or above) in the study eye;
- Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye; and
- History of other disease, metabolic dysfunction, physical examination finding, 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, ¶141; Ex.1097).

8. Heimann-2007 (Ex.1040)

Heimann-2007 published in 2007, and thus is prior art under 35 U.S.C. § 102.

Heimann-2007 discloses guidelines and strategies for the administration of intravitreal injections. Heimann-2007 discloses 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, ¶143; Ex.1097). 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." (Ex.1040, 67).

Heimann-2007 discloses in Table 5.1 a number of complications that may result from intravitreal injections, including endophthalmitis, keratitis, intraocular inflammation, and uveitis/pseudo-endophthalmitis. (Ex.1040, 68).

Heimann-2007 discloses endophthalmitis as one of "the most serious side effects of intravitreal injections" and that "[o]ther important, potentially sight-threatening complications of injections are intraocular inflammation…" (Ex.1040, 69, 74-75). Heimann-2007 also discloses uveitis and pseudo-endophthalmitis as potential inflammation-related complications. (Ex.1040, 75).

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. (Ex.1040, 76). Heimann-2007 instructs 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" and that "preparation of the ocular surface should aim to minimize bacterial contamination during the injection." (Ex.1040, 76; Ex.1002, ¶¶143-44; Ex.1097).

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." (Ex.1040, 81). Heimann-2007 concludes with instructions to "[e]xclude patients with suspected bacterial infections of the anterior segment (e.g., blepharitis, conjunctivitis)." (Ex.1040, 85; Ex.1002, ¶143; Ex.1097).

XII. GROUNDS FOR UNPATENTABILITY – DETAILED ANALYSIS.

A. ANTICIPATION

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

1. Legal Standards.

Anticipation requires a "single prior art reference disclose[], either expressly or inherently, each limitation of the claim." *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002).

A 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 benefits of a known process are not patentable because they 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" inherently anticipated because "[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").

"[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to one of skill in the art." *Bristol-Myers*, 246 F.3d 1379. Here, the independent claims require only a dosing regimen without any particular efficacy or result (Ex.1002, ¶¶47-52; Ex.1097), 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 34 are anticipated by Dixon, as shown in the following tables, and confirmed by Dr. Albini (Ex.1002, ¶¶145-53; *see also* Ex.1097):

Claim 1:	**Dixon:**
A method for treating age related macular degeneration in a patient in need thereof,	"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).
comprising intravitreally administering, to said patient,	"The safety, tolerability and biological activity of intravitreal VEGF Trap-Eye in treatment of neovascular AMD was evaluated in the two-part Clinical Evaluation of Anti-angiogenesis in the Retina-I (CLEAR-IT-I) study." (*Id.*). "[VIEW 1] will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye…" (*Id.*, 1576).
an effective amount of aflibercept which is 2 mg	Patients treated with monthly loading doses of 2.0 mg followed by PRN dosing "achieved mean improvements of 9.0…ETDRS letters with 29%...gaining… ≥ 15 ETDRS letters at 52 weeks." (Id., 1576). Patients in this arm also displayed mean decreases in retinal thickness of 143 μM compared to baseline. (*Id.*) "One promising new [angiogenesis inhibiting] drug is aflibercept (VEGF Trap-Eye), a fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2." (*Id.*, 1573 (Abstract)). "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure." (*Id.*, 1575).
approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.	"[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 (emphasis added)).

The analysis for **Claim 34** is similar:

Claim 34:	**Dixon:**
A method for treating an angiogenic eye disorder in a patient in need thereof,	"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 (describing DME and RVO studies)).
said method comprising administering to the patient an effective sequential dosing regimen of a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist	"[Phase 3] will evaluate the safety and efficacy of . . . 2.0 mg at an 8 week dosing interval (following three monthly doses)." (Ex.1006, 1576 (emphasis added)). In other words, an "initial dose" at day 0, "secondary doses" at weeks 4 and 8; and "tertiary doses" of every 8 weeks beginning at week 16 (i.e., doses at weeks **0, 4, 8**, **16, 24, 32, 40, and 48**).
wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and	(*Id.*). (i.e., the doses at weeks **0, 4, 8**).
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	(*Id.*). (i.e., the doses at weeks **16, 24, 32, 40, and 48**).

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component	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).

(Ex.1002, ¶¶152-53; Ex.1097).

Claims 2, 8, 42, and 43 further claim neovascular (wet) AMD or AMD. Dixon discloses administering VEGF Trap-Eye to patients with neovascular AMD. (Ex.1006, 1573, 1576 ("~1200 patients with neovascular AMD"); Ex.1002, ¶¶158-60, 184-86; Ex.1097).

Claims 3 and 4 recite "wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score" and "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." Dixon discloses that in phase 2 "[p]atients initially treated with 2.0 … mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) … ETDRS [BCVA] letters with 29[%] … gaining … ≥ ~15 ETDRS letters at 52 weeks." (Ex.1006, 1576). A gain of ≥ ~15 ETDRS BCVA letters necessarily encompasses a loss of less than 15 letters. (Ex.1002, ¶162; Ex.1097).

Dixon also discloses that for phase 3 (VIEW) "the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters)." (Ex.1006, 1576; Ex.1002, ¶162; Ex.1097).

In addition, the claimed visual acuity measures do not distinguish the claimed dosing regimens from prior art disclosing the same regimens. Claim 1 (from which claims 3 and 4 depend) covers the dosing regimen used in the VIEW trial; the same dosing regimen was disclosed in Dixon (in related proceedings, PO never disputes this). (Ex.1002, ¶163; Ex.1097). "[B]ecause the prior art methods in their 'normal and usual operation…perform the function which [PO] claims in [the '601 patent], then such [patent] will be considered, to have been anticipated by the [prior art].'" *King Pharms.*, 616 F.3d at 1276 (quoting *In re Ackenbach*, 45 F.2d 437, 439 (C.C.P.A. 1930)); *see also, e.g.*, *Perricone*, 432 F.3d at 1380 ("Using the same composition claimed by Dr. Perricone in the same manner claimed by Dr. Perricone naturally results in the same claimed skin benefits.").

Claims 5 and 6 recite "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score" and "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score." Dixon discloses that in phase 2 "[p]atients initially treated with 2.0…mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 (p <

0.0001)…ETDRS [BCVA] letters with 29[%]…gaining…≥ ~ 15 ETDRS letters at 52 weeks." (Ex.1006, 1576; Ex.1002, ¶167; Ex.1097).

In addition, for the reasons stated above for claims 3 and 4, Dixon disclosed the same VIEW clinical trial regimen with the same drug now claimed in claim 1 (from which claims 5 and 6 depend). (Ex.1002, ¶¶168-69; Ex.1097). "[B]ecause the prior art methods in their 'normal and usual operation…perform the function which [PO] claims in [the '601 patent], then such [patent] will be considered, to have been anticipated by the [prior art].'" *King Pharms.*, 616 F.3d at 1276 (quoting *Ackenbach*, 45 F.2d at 439); *see also, e.g.*, *Perricone*, 432 F.3d at 1380.

Claim 7 recites "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly." As discussed above, Dixon discloses "[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 (emphasis added); Ex.1002, ¶¶154-57; Ex.1097).

Claims 9 and 36 recite "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection." The recited exclusion criteria are entitled no patentable weight, as Petitioner explains above. Regardless, excluding patients exhibiting the recited exclusion criteria was a necessary, and thus inherent outcome, of the protocol of the VIEW clinical trials disclosed in Dixon. (Ex.1018, Appx. 2-3; Ex.1002, ¶¶175-76; Ex.1097). For

example, the 1200 patients Dixon discloses as being enrolled in the VIEW trials necessarily will have been screened for all inclusion and exclusion criteria, and determined to not be exhibiting any of the exclusion criteria, including those claimed.

Claim 35 limits the method to "aflibercept." As discussed above, Dixon discloses that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure," (Ex.1006, 1575), and are the same molecule: "***One*** promising new [angiogenesis inhibiting] drug is aflibercept (VEGF Trap-Eye), ***a*** fusion protein that blocks all isoforms of VEGF-A and placental growth factors-1 and -2," (*id.*, 1573 (Abstract) (emphasis added); Ex.1002, ¶172; Ex.1097; *see also, e.g.*, *supra* § XI(A)).

Claims 37 and 38 further 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, ¶¶69, 179; Ex.1097; Ex.1001, 2:47-50 ("Various administration routes are contemplated…including…intraocular administration (e.g., intravitreal administration).")). Dixon disclosed that VIEW will evaluate "the safety and efficacy of intravitreal VEGF Trap-Eye." (Ex.1006, 1576).

Claims 39, 41, and 45 recite "2 mg" of VEGF antagonist. Dixon discloses the use of 2.0 mg VEGF Trap-Eye doses with the VIEW dosing regimen. (Ex.1006, 1576 ("2.0 mg at an 8 week dosing interval (following three monthly doses"); Ex.1002,

¶¶181-83; Ex.1097). Dixon explains that the 2 mg intravitreal dose "allows for extended blocking of VEGF in the eye, but would be predicted to give negligible systemic activity as it will be rapidly bound to VEGF and inactivated." (Ex.1006, 1575).

* * *

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

3. Grounds 2, 3, and 4: Adis, Regeneron (8-May-2008), and NCT-795 anticipate the Challenged Claims.

Independent Claims 1 and 34 are anticipated by Adis, Regeneron (8-May-2008), and NCT-795, which, as shown below, and confirmed by Dr. Albini (Ex.1002, ¶¶187-94, 226-32, 265-68; *see also* Ex.1097), disclose each and every element:

Claim 1:	**Prior Art:**
A method for treating age related macular degeneration in a patient in need thereof,	Preamble is non-limiting. **Adis:** "Regeneron and Bayer are developing the agent [i.e., aflibercept] for eye disorders." (Ex.1007, 261, 263).
	Regeneron (8-May-2008): "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) will enroll approximately 1,200 patients." (Ex.1013, 1).
	NCT-795: "Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration." (Ex.1014, 1, 4).
comprising intravitreally administering, to said patient,	**Adis:** "The non-inferiority, [VIEW1]…study will evaluate the safety and efficacy of intravitreal aflibercept" (Ex.1007, 263).

an effective amount [7] of aflibercept which is 2 mg	"2.0 mg at an 8-week dosing interval…" (Ex.1007, 263).
	Regeneron (8-May-2008): "Both VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection." (Ex.1013, 1). "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, 1).
	NCT-795: "…Repeated Doses of Intravitreal VEGF Trap…" (Ex.1014, 3). "2.0 mg VEGF Trap-Eye administered every 8 weeks…" (Ex.1014, 8).
approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.	**Adis:** "[VIEW 2] will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at . . . *2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4*." (Ex.1007, 263 (emphasis added)).
	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 (emphasis added)).
	NCT-795: "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (Ex.1014, 8).

[7] The claims expressly define "an effective amount" as 2.0 mg which was disclosed in the prior art. Accordingly, Adis, Regeneron (8-May-2008), and NCT-795 disclose that element through their disclosures of the administration of 2.0 mg of VEGF Trap-Eye/aflibercept.

	In other words, doses at weeks **0, 4, 8, 16, 24, 32, 40, and 48**. (Ex.1002, ¶¶187-92, 226-30, 265-66; Ex.1097).

Claim 34:	**Prior Art:**
A method for treating an angiogenic eye disorder in a patient in need thereof,	Preamble is non-limiting. **Adis:** "Regeneron and Bayer are developing the agent [i.e., aflibercept] for eye disorders." (Ex.1007, 261). "A second phase III trial (VIEW 2) in wet AMD began with the first patient dosed in May 2008." (*Id.*).
	Regeneron (8-May-2008): "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) will enroll approximately 1,200 patients." (Ex.1013, 1).
	NCT-795: "Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration." (Ex.1014, 1, 4).
said method comprising administering to the patient an effective sequential dosing regimen[8] of a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more	**Adis:** "[VIEW 2] will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at . . . 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Ex.1007, 263).
	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).

[8] The claims expressly define an effective sequential dosing regimen as having the recited steps. Adis, Regeneron (8-May-2008), and NCT-795 disclose that element via disclosure of VIEW (every-8-week, "Q8") regimen.

tertiary doses of the VEGF antagonist; wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered 8 weeks after the immediately preceding dose;	**NCT-795:** "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (Ex.1014, 8). In other words, doses at weeks **0, 4, 8, 16, 24, 32, 40, and 48**. (Ex.1002, ¶¶187-92, 226-30, 265-66; Ex.1097).
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component.	**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 IgG1." (Ex.1007, Abstract). **Regeneron (8-May-2008):** Discloses "VEGF Trap-Eye," which a POSA understood to have the recited domains. (Ex.1013, 1-2; Ex.1006, Fig. 1). **NCT-795:** Discloses "VEGF Trap-Eye," which a POSA understood to have the recited domains. (Ex.1014, 1, 4, 8; Ex.1006, Fig. 1). (Ex.1002, ¶¶193, 231, 267; Ex.1097).

Claims 2, 8, 42, and 43 recite neovascular (wet) AMD or AMD. Adis discloses the "trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD." (Ex.1007, 263; Ex.1013, 1; Ex.1014, 3; Ex.1002, ¶¶198-200, 222-24, 236-38, 262-64, 272-74, 298-300; Ex.1097).

Claims 3, 4, 5, and 6. Adis, Regeneron (8-May-2008), and NCT-795 disclose the same dosing regimen and same drug claimed in claim 1 (from which claims 3-6 depend). "[B]ecause the prior art methods in their 'normal and usual operation…perform the function which [PO] claims in [the '601 patent], then such

[patent] will be considered, to have been anticipated by the [prior art].'" *King Pharms.*, 616 F.3d at 1276 (quoting *Ackenbach*, 45 F.2d at 439); *see also, e.g.*, *Perricone*, 432 F.3d at 1380.

Lastly, NCT-795 expressly discloses the VIEW primary outcome measure of "[t]he proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline," and disclose one of the VIEW secondary outcome measures as "[t]he proportion of subjects who gain at least 15 letters of vision at Week 52." (Ex.1014, 9; *see also, e.g.*, Ex.1013, 1). ETDRS is a well-known measure of BCVA. (Ex.1002, ¶¶201-08, 239-48, 275-84; Ex.1097).

Claim 7. As discussed above, Adis discloses that the VIEW trials will involve aflibercept administered "at an 8 week dosing interval, including one additional 2.0 mg dose at week 4," i.e., the first three doses at 4 week intervals. (Ex.1007, 263; *see also, e.g.*, Ex.1013, 1; Ex.1014, 8). A POSA would understand 4-week dosing intervals to comprise "approximately every 28 days or approximately monthly." (Ex.1002, ¶¶195-97, 233-35, 269-71; Ex.1097).

Claims 9 and 36. The recited exclusion criteria are entitled no patentable weight, as Petitioner explains above. Regardless, excluding patients exhibiting the recited exclusion criteria was a necessary, and thus inherent outcome, of the protocol of the VIEW clinical trials disclosed in Adis, Regeneron (8-May-2008), and NCT-

795. (Ex.1018, 2540). For example, the references disclose that the VIEW trial will enroll approximately 1200 patients. Each of these 1200 patients necessarily will have been screened for all inclusion and exclusion criteria, and determined to not be exhibiting any of the exclusion criteria, including those claimed.

Claim 35. As discussed above, Adis discloses the VIEW trials' evaluation of "the safety and efficacy of intravitreal aflibercept." (Ex.1007, 263; *see also, e.g.*, Ex.1013, 1 ("VEGF Trap-Eye"); Ex.1014, 1 (same)).

Claims 37 and 38. Intravitreal administration is a subset of intraocular administration. (Ex.1002, ¶¶69, 179; Ex.1001, 2:47-50; Ex.1097). Adis, Regeneron (8-May-2008), and NCT-795 disclose these elements. (Ex.1007, 263; *see also id.*, 263-264 ("intravitreal injection as a route of administration"); *id.*, 265-66 (Table II); *id.*, 268 (Phase 1 trials in AMD with intravitreal aflibercept); Ex.1013, 1; Ex.1014, 3; Ex.1002, ¶¶216-18, 256-58, 292-94; Ex.1097).

Claims 39, 41, and 45. Adis discloses "intravitreal aflibercept at doses of…2.0 mg." (Ex.1007, 263; *see also, e.g.*, Ex.1013, 1 ("2.0 mg"); Ex.1014, 6-7; Ex.1002, ¶¶219-21, 259-61, 295-97; Ex.1097).

* * *

Accordingly, Adis, Regeneron (8-May-2008), and NCT-795 disclose the limitations of each of the challenged claims, and thus anticipate.

* * *

Each anticipatory reference asserted herein is presumed enabling and it is PO's burden to rebut those presumptions. *See, e.g.*, *In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012); *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 659-60 (D. Del. 2014) (rejecting patentee non-enablement arguments where reference disclosed exact dosing amount and interval in claims, thus inherently disclosing the claimed "minimizing skeletal muscle toxicity"). Rebuttal here would be futile because each reference clearly sets forth a dosing regimen that a POSA would have no trouble following. Moreover, the Challenged Claims' preamble—even if assumed limiting—does not help PO; nor would Regeneron's potential proposed construction of "tertiary dose," should PO attempt to propose the construction in this IPR that it proposed in IPR2021-00881. The VEGF Trap-Eye/aflibercept Phase 2 data show "treating" of AMD with VEGF Trap-Eye; treating which was accomplished using even fewer doses, on average, than the VIEW Q8 regimen. (Ex.1006, 1576; Ex.1007, 267-68; Ex.1013, 1-2; Ex.1014, 7). Further, "[n]ewly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." *Bristol-Myers*, 246 F.3d at 1376. In addition to the Phase 2 data, inherency is illustrated by the VIEW Q8 dosing results. (Ex.1018, 2541-45). From these results the authors concluded that "aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections." (*Id*., 2537). *Geneva Pharms.,*

Inc. v. Glaxosmithkline PLC., 213 F. Supp. 2d 597, 607 (E.D. Va. 2002) ("GSK argues that the Cole '552 patent was not anticipated by the Crowley '609 patent because clavulanic acid does not effectively inhibit β-lactamase enzymes one hundred percent of the time. The Court does not adopt GSK's attempt to raise the bar by redefining what is meant by inherent as that term is used in deciding anticipation."), *aff'd*, 349 F.3d 1373 (Fed. Cir. 2003).

B. OBVIOUSNESS

The Challenged Claims also would have been 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 5: 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 and thus anticipates them. Separately, Dixon also renders the Challenged Claims obvious in light of the POSA's (i) knowledge of the molecule VEGF Trap-Eye/aflibercept; (ii) clear motivation—as expressly stated in Dixon—to use less frequent dosing; and (iii) reasonable expectation of success from Dixon's disclosure of the positive Phase 2 trial data for VEGF Trap-Eye. (Ex.1002, ¶¶301-43; Ex.1097).

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

Second, numerous Regeneron publications and patent submissions disclosed the VEGF Trap-Eye domain composition, including the '758 and '173 patents. (*See, e.g.*, Ex.1010, Fig.24A-C; *id.*, 15:50-16:6; Ex.1008, 1:48-52; Ex.1002, ¶¶134-37,

312; Ex.1097). As described above, those patents, along with the Holash 2002 article and the body of VEGF Trap-Eye and aflibercept literature that refers back to Holash 2002, would have informed a POSA regarding the identity and domain composition of VEGF Trap-Eye/aflibercept. (*See supra* § XI(A)).

Third, prior to 2011, a known problem in treating AMD existed for which the prior art taught an obvious solution. *See 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 of cataract, intraocular inflammation, retinal detachment and endophthalmitis."); Ex.1002, ¶¶111, 302; Ex.1097). Thus, Dixon disclosed motivation to employ extended dosing regimens and taught a dosing regimen featuring longer dosing intervals: the VIEW Phase 3 clinical trial regimen—*i.e.*, an obvious solution to the need for less frequent injections.[9] (Ex.1006, 1576; Ex.1002, ¶¶302-03; Ex.1097). In other words, Dixon "go[es] beyond just illuminating a known problem; [it] also expressly propose[s] the

[9] Dixon discloses 8-week dosing with 2 mg of VEGF Trap-Eye/aflibercept following three monthly doses, (Ex.1006, 1576), *i.e.*, dosing every 4 weeks for three months, followed by every 8 weeks (Claim 1), *i.e.*, a single initial dose, followed by one or more secondary doses every 4 weeks, followed by one or more tertiary doses every 8 weeks (Claim 34).

claimed solution." *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1375-76 (Fed. Cir. 2013).

Fourth, a POSA would reasonably expect success administering the VIEW1/VIEW2 regimens. No specific efficacy is required of independent claims 1 and 34[10]; however, the Phase 2 CLEAR-IT-2 results disclosed in Dixon, which showed mean improvements of 9.0 letters in BCVA using even fewer doses per year than the Phase 3 VIEW regimen, would have provided a POSA with a reasonable expectation of success, and would have been an inherent aspect of the prior art, which set forth use of the same molecule with the same dosing regimen claimed in claims 1 and 34.

Accordingly, Dixon renders obvious independent claims 1 and 34 of the '601 patent, for the reasons discussed above. (*See supra* § XII(A)(2)). Dixon also renders obvious:

[10] To the extent PO points to the "effective amount" or "effective" language in claims 1 and 34, the claims expressly define that effective amount as 2 mg and an effective dosing regimen as the one claimed, both features that were already disclosed in the prior art. (Ex.1001, 21:41-46, 24:4-19). Accordingly, Dixon discloses those elements through its disclosure of the administration of 2.0 mg of aflibercept and the VIEW dosing regimen. (Ex.1006, 1576).

- claims 2, 8, 42, and 43 through its disclosure of the VIEW treatment of "Wet age-related macular degeneration," (Ex.1006, 1576);
- claim 7 through its disclosure of the VIEW "monthly" loading doses, (Ex.1006, 1576);
- claims 9 and 36 through its disclosure of the risks from intravitreal injections of intraocular inflammation and endophthalmitis, (Ex.1006, 1577);
- claim 35 through its disclosure of aflibercept, (Ex.1006, 1573, 1575, 1576 (Fig. 1));
- claims 37-38, 39, 41, and 45, through its disclosure of VIEW's evaluation of "intravitreal VEGF Trap-Eye at doses of…2.0 mg." (Ex.1006, 1576 (emphasis added)).

With respect to claims 3-6, which require that a patient loses less than, or gains at least, 15 letters of BCVA ETDRS score, those claim elements are inherent because the prior art discloses using the same drug in the same way as claims 1 and 34. *Perricone*, 432 F.3d at 1380. However, those elements also are obvious in view of Dixon's disclosure of the use of said measures in VIEW and CLEAR-IT-2 (Ex.1006, 1576), and a POSA would have had a reasonable expectation of success at achieving those BCVA criteria, based upon the results of the Phase 2 clinical trials. As Dixon reports, in the Phase 2 CLEAR-IT-2 AMD trial, "[p]atients initially treated with 2.0…mg of VEGF Trap-Eye monthly achieved mean improvements of

9.0…ETDRS letters" with 29% gaining ≥ 15 ETDRS letters at 52 weeks, with a regimen employing *even fewer doses* than the number planned for the Phase 3 VIEW trials.[11] (Ex.1006, 1576; Ex.1002, ¶¶320-25; Ex.1097). Section 103 "does not require absolute predictability of success," *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), but only a POSA's *reasonable* expectation that it would work for its intended purpose, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). 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, rendering obvious the Challenged Claims, alone, or in view of the '758 or '173 patents (which disclose the domain composition and sequences of aflibercept).

3. Grounds 6 and 7: Claims 9 and 36 are obvious over Dixon in combination with Rosenfeld-2006 (Ground 6), or in combination with Heimann-2007 (Ground 7) (and if necessary, in combination with the '758 and '173 patents).

For the reasons presented above, Dixon alone or with the '758 or '173 patents, renders obvious each of the Challenged Claims, including claims 9 and 36. However,

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[11] Phase 2 (CLEAR-IT-2): 4 monthly injections + 1.6 as-needed injections = 5.6 injections/year.

Phase 3 (VIEW1/2): 3 monthly injections + 5 bimonthly injections = 8 injections/year.

claims 9 and 36 also are obvious in view of Dixon in combination with prior art, such as Rosenfeld-2006 or Heimann-2007, disclosing exclusion of patients from receiving intravitreal injections where those patients have ocular or periocular infections, or signs of such infection (i.e., inflammation).

Exclusion Criteria. The recited exclusion criteria are not entitled to patentable weight, as discussed above (*see supra* § IX(C)), but are nonetheless disclosed in the prior art. For example, a review of other major anti-VEGF AMD clinical trials before 2011 reveals the use of nearly identical exclusion criteria to that used in VIEW and set forth in the '601 patent. Rosenfeld-2006 reports the results of the seminal MARINA Phase 3 clinical trial assessing monthly intravitreal LUCENTIS (ranibizumab) in the treatment of AMD, and includes a Supplementary Appendix providing additional information about the trial, including eligibility criteria, among which were several exclusion criteria directed to infection and inflammation:

- "Active intraocular inflammation (grade trace or above) in the study eye."
- "Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye."
- "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, ¶347; Ex.1097).

Conjunctivitis, keratitis, scleritis, and endophthalmitis are well-known among POSAs as ocular and/or periocular types of infections. (Ex.1002, ¶¶95, 348; Ex.1097; Ex.1040, 67, 76-77, 85).

Given the known risks associated with intravitreal injections, POSAs administering intravitreal injections would have been motivated to follow Rosenfeld-2006, and exclude patients that were showing signs of infection or potential infection (i.e., "intraocular inflammation"), in order to avoid exacerbating existing conditions. (Ex.1002, ¶¶346, 348; Ex.1097). Further, a POSA would have understood that injecting an eye with existing inflammation/infection events also could confound the physicians' analysis of the clinical efficacy of aflibercept. (Ex.1002, ¶¶348-49; Ex.1097).

In addition, in the aflibercept VIEW trials, one of the primary aims was to assess the non-inferiority of aflibercept compared to monthly ranibizumab. (Ex.1006, 1575 ("This non-inferiority study will evaluate…VEGF Trap-Eye…compared with 0.5 mg of ranibizumab administered every 4 weeks.")). Thus, a POSA would have been motivated to adopt ranibizumab MARINA exclusion criteria when running a clinical trial comparing aflibercept and monthly ranibizumab, because of the desire to maintain consistency of the patient populations for statistical comparison purposes. (Ex.1059, 953; Ex.1002, ¶348; Ex.1097). POSAs would have been aware that "[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," and that "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 (emphasis added)). In other words, it would have been obvious to use the same or very similar set of eligibility criteria in VIEW as were used in MARINA/ANCHOR. (Ex.1002, ¶348; Ex.1097).

In addition, a POSA would have been motivated to avoid injecting infected or inflamed eyes based on well-known guidelines for intravitreal injections. For example, Heimann-2007 advises that "[b]acterial infections of the anterior segment and ocular adnexa increase the risk of endophthalmitis and should be treated *before performing an intravitreal injection*." (Ex.1040, 81 (emphasis added), 85 ("Exclude patients with suspected bacterial infections or the anterior segment (e.g., blepharitis, conjunctivitis).")). Indeed, as POSAs recognized, and Heimann-2007 discloses, "[e]ndophthalmitis is the most feared complication of intravitreal injections," (*id*., 67), due to its "potentially devastating consequences," (*id.*, 76). Heimann-2007 also discloses that "severe intraocular inflammatory reactions can be seen" following intravitreal injections, and that it can be "extremely difficult, to differentiate a sterile inflammatory process from an inflammatory reaction associated with infectious endophthalmitis." (*Id*., 75).

Accordingly, for the reasons discussed above, the disclosures of Dixon, combined with those of Rosenfeld-2006 (Ground 6) and Heimann-2007 (Ground 7), and if necessary, the '758 or '173 patents, make obvious the exclusion of patients with ocular or periocular infection or exhibiting signs of potential infection (i.e., inflammation).

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 1-4, and they cannot overcome the strong *prima facie* case of obviousness presented in Grounds 5-7. *See Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

If Regeneron alleges that the VIEW1/VIEW2 regimen in Example 4, as disclosed in Heier-2012 (Ex.1018, 2537), yielded unexpected results, that argument should be rejected. The same regimen already was in the prior art, as were the phase 2 results obtained by Regeneron. Phase 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 Phase 3 every-eight-week regimen (8 injections/year). (Ex.1006, 1576). From this, Regeneron announced that "an 8-week dosing schedule may be feasible." (Ex.1012, 1; Ex.1003, ¶¶44-47, 56-63, 76-78; Ex.1002, ¶¶354-58; Ex.1097).

To the extent Regeneron argues long-felt but unmet need, it will be unable to establish a "need" or show that any such need was "long-felt." By 2009, the claimed dosing regimen was already publicly disclosed by Regeneron itself, and thus any "unmet" need had already been fulfilled before the '601 patent was filed. (Ex.1002, ¶359; Ex.1097). PO's experts in related IPRs, and other ophthalmologists, have been implementing regimens like those claimed since well before 2011. (Ex.1090, 2 (Dr. Brown: "I give 3 monthly injections and see them in 8 weeks")).

To the extent Regeneron characterizes the standard of care at the time as monthly dosing in order to emphasize the purported unexpectedness of the 8-week dosing regimen, this ignores the actual practice of ophthalmologists at the time, who had begun using PRN or treat-and-extend dosing after a series of monthly loading doses. (Ex.1002, ¶¶355, 358; Ex.1097; Ex.1090, 2 ("I give 3 monthly injections and see them in 8 weeks."); Ex.1025, 1369 ("PrONTO-style dosing has become popular.")).

Should Regeneron allege commercial success, Regeneron will be unable to establish that the success is attributable to the claimed regimens, (Ex.1002, ¶360; Ex.1097). PO's proofs in a related IPR were deficient for a host of reasons, including, but not limited to, failure to tie the claimed regimen to 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: February 10, 2023

Respectfully submitted,

By /Raymond N. Nimrod/

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the forgoing Petition for *Inter Partes* Review of U.S. Patent No. 10,888,601 complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(i) and (b)(i) permitting a preliminary response of up to 14,000 words because, exclusive of the exempted portions, it contains 13,980 words as counted by the word processing program used to prepare the paper.

Date: February 10, 2023

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CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that true and correct copies of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 10,888,601, Exhibits 1001-1101, and Motion for Joinder were served on February 10, 2023 via FedEx Priority Overnight on Patent Owner at the correspondence address of record for U.S. Patent No. 10,888,601 as evidenced in Patent Center:

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