UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC., CELLTRION, INC.,
and APOTEX, INC.,
Petitioners

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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Case IPR2021-00881[1]
Patent No. 9,254,338 B2

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# PATENT OWNER RESPONSE

[1] IPR2022-00258 and IPR2022-00298 have been joined with this proceeding.

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Patent Owner Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron") respectfully submits that Petitioner Mylan Pharmaceuticals Inc. ("Petitioner" or "Mylan") has not carried its burden of demonstrating by a preponderance of the evidence that Claims 1, 3-11, 13-14, 16-24 and 26 ("the Challenged Claims") of U.S. Patent No. 9,254,338 ("the '338 Patent," Ex.1001) are unpatentable.

## I. INTRODUCTION

Over the course of many years, Regeneron developed and tested novel anti-VEGF fusion proteins composed from VEGF receptor domain sequences, which could catch, hold, and block ("trap") circulating VEGF. These "VEGF Traps" had the potential to treat angiogenic disorders, including cancers and diseases of the eye. Regeneron partnered with Sanofi to develop a VEGF Trap for oncology and shortly thereafter, Regeneron (and its partner Bayer) developed a VEGF Trap for angiogenic eye disorders.

In 2011, FDA first approved the VEGF Trap now known as EYLEA® for the treatment of wet age-related macular degeneration ("wAMD"). Despite launching into a competitive market, EYLEA quickly became the preeminent treatment for angiogenic eye disorders including wAMD, diabetic macular edema, macular edema following retinal vein occlusion, and diabetic retinopathy. Ex.2052 (Manning Decl.), ¶¶29-42, 48-85.

Before EYLEA, ranibizumab (Lucentis®) or off-label bevacizumab

(Avastin®) were the standard-of-care for treatment of angiogenic eye disorders. While both ranibizumab and bevacizumab provided highly effective treatment, the great burden of monthly eye injections or office visits led to extensive efforts in the art to decrease injection frequency and physician monitoring. Ex.1018, 1, 9. But fixed quarterly and "as needed" (*pro re nata*) dosing regimens without monthly monitoring visits were not effective at maintaining vision. Ex.1018, 1.

Regeneron's Phase III clinical trial results in wAMD surprisingly demonstrated "remarkably similar improvement in vision and anatomic measures can be achieved" with less frequent dosing of EYLEA as compared to monthly injections of ranibizumab. Ex.1012, 10-11. By satisfying this long-felt but unmet need in the art to reduce treatment burden and injection frequency, EYLEA has enjoyed rapid clinical adoption and great commercial success. Ex.2050, ¶¶151-159; Ex.2052, ¶¶48-104.

Mylan's novelty and obviousness challenges rely entirely on references disclosing the design of Regeneron's own ***prospective*** Phase 3 trials. But Mylan's expert, Dr. Albini, admitted that before Regeneron's trials, no one used the claimed dosing and, further, that an existing dosing regimen with monthly monitoring, albeit more burdensome, would have been considered a "better dosing strategy" than Regeneron's prospective once-per-eight-weeks ("Q8") dosing regimen given the failures with extended dosing in the art. Ex.2130 (Albini Tr.), 283:13-284:7, 285:15-286:3. Thus, Mylan's suggestion that Regeneron's claimed Q8 dosing

regimen, first tested in its Phase 3 trials, lacked novelty or was obvious is undermined by the great uncertainty that existed as to whether a Q8 extended, fixed dosing regimen would work until Regeneron's Phase 3 clinical trial results proved that it could.

## II. THE STATE OF THE ART

Angiogenic eye disorders, such as neovascular age-related macular degeneration ("wet AMD" or "wAMD"), diabetic macular edema ("DME") and macular edema following retinal vein occlusion ("RVO"), are characterized by abnormal growth or permeability of blood vessels in the retina and elevated ocular levels of VEGF. Ex.2050 (Brown Decl.), ¶¶26-28. Early treatments for wAMD, such as laser ablation and photodynamic therapy ("PDT"), only slowed eventual vision loss. *Id*., ¶27. By the early 2000's, researchers began to investigate anti-VEGF agents to treat angiogenic eye disorders. Macugen® was the first anti-VEGF agent approved for treatment of angiogenic eye disorders, specifically wAMD, but like laser and PDT treatments, it only slowed the rate of vision loss. *Id*., ¶30.

Clinical testing of Genentech's drug, ranibizumab (Lucentis®), established the potential therapeutic benefit of anti-VEGF therapy. Ex.2050, ¶31; Ex.2051, ¶51. The Lucentis clinical trials showed for the first time that patients with wAMD could experience ***vision gains*** (7-9 letters on average) as opposed to merely slowing vision loss. Ex.2050, ¶¶31-39 (noting quality of life importance of vison gains);

Ex.2051 (Do Decl.), ¶¶60-64; Ex.2130 (Albini Tr.), 28:18-29:3. Shortly after its approval in June 2006, Lucentis (or off-label Avastin)[2] became the prevailing standard-of-care for treatment of angiogenic eye disorders. Ex.2050, ¶40-42; Ex.2051, ¶54, 65-68; Ex.2130 (Albini Tr.), 153:2-6 (Lucentis and off-label Avastin as standard of care by 2011).

After this development, merely slowing disease progression was no longer considered to be effective treatment for angiogenic eye disorders and, consequently, use of Macugen all but disappeared. Ex.2050, ¶42; Ex.2051, ¶¶65-68; Ex.2130 (Albini Tr.), 155:10-17, 156:11-157:11; 193:19-194:15; Ex.1006 (Dixon), 1574. As Mylan's expert, Dr. Albini, aptly put it, by 2011, Macugen was "ancient history." Ex.2130 (Albini Tr.), 28:18-29:3. Instead, the standard-of-care for wAMD quickly moved to frequent intravitreal injections of Lucentis (or off-label Avastin), which could improve patients' vision and often maintain those gains over the course of treatment. Ex.2050, ¶¶40-42; Ex.2051, ¶¶66-68; Ex.2130 (Albini Tr.), 153:2-6 (Lucentis and off-label Avastin as standard of care by 2011).

Nonetheless, the risk of rare but serious adverse events from intravitreal

[2] Avastin® (bevacizumab), an anti-VEGF antibody, was approved by FDA for the treatment of metastatic colorectal cancer in February 2004. Ex.2156. By late 2005, however, ophthalmologists had reported successfully using Avastin off-label for the treatment of wAMD. Ex.2050, ¶¶29, 40.

injections, together with the significant burden of monthly office visits, led to extensive efforts in the art to decrease injection and monitoring frequency. Ex.2050, ¶¶45, 151-155; Ex.1018, 2537. Numerous attempts were made to decrease injection or monitoring frequency with ranibizumab, including the PIER, PrONTO, SAILOR, EXCITE, and SUSTAIN clinical trials. Ex.2050, ¶¶46-69, 160-164. Each of these efforts at extended dosing in the art failed because they were not effective at maintaining vision. *Id*.; Ex.1018, 2537.

PIER, EXCITE, and SAILOR[3] tested fixed quarterly dosing of ranibizumab. Each study reported that initial visual acuity gains from monthly loading doses were lost over the quarterly maintenance period. Ex.2130 (Albini Tr.), 234:5-6, 234:12-19, 237:1-7; Ex.2050, ¶¶47-62, 68. Not surprisingly, fixed quarterly dosing of ranibizumab was never adopted in clinical practice. Ex.1018, 2537; Ex.2130 (Albini Tr.), 33:12-34:12; 237:8-15; Ex.2050, ¶68. PrONTO, a 40 patient, non-randomized study, ***required 24 dilated office visits in the first year*** with injections given on an as needed basis. Ex.2050, ¶¶63-67. Even so, subjects in PrONTO experienced vision-threatening complications despite close monitoring. *Id*.; Ex.2130 (Albini Tr.), 254:11-19. SUSTAIN, which tested PRN maintenance

[3] SAILOR tested three monthly loading doses followed by PRN with quarterly monitoring visits such that study subjects could not receive retreatment more frequently than once quarterly. Ex.2130 (Albini Tr.), 235:20-236:13.

dosing, reported loss of visual acuity gains in the PRN maintenance period. Ex.2050, ¶¶67-68. Ultimately, these efforts to develop extended dosing regimens led to inferior results (*i.e.*, loss of visual acuity, vision-threatening complications) as compared to monthly dosing with ranibizumab. *Id.*, ¶¶68-69.

Despite enormous efforts, before the inventive method of the '338 Patent, no one had been able to extend the dosing interval while maintaining the high level of efficacy of the standard-of-care—*i.e.*, Lucentis or off-label Avastin. Ex.2050, ¶69; Ex.1018, 2545.

## III. THE '338 PATENT

The '338 Patent is directed to therapeutic treatments for angiogenic eye disorders using the recited dosing regimens. Ex.1001, Title, Abstract, 1:1-2, 1:15-20; 1:48-9, 1:50, 1:52, 2:23-24, 2:42-45, 3:19-20, 4:33-37, 5:12-29, 7:16-19, 9:18-20, 23:2-3, 24:3-4. The '338 specification notes that "FDA-approved treatments of angiogenic eye disorders such as AMD and CRVO include the administration of an anti-VEGF antibody called ranibizumab (Lucentis®, Genentech, Inc.) on a monthly basis by intravitreal injection." Ex.1001, 1:49-59. Nonetheless, the Patent states: "***there remains a need in the art for new administration regimens for angiogenic eye disorders, especially those which allow for less frequent dosing while maintaining a high level of efficacy***." *Id.* (emphasis added). Thus, the '338 Patent identifies the problem at hand—to find a treatment method that provides a "high level of efficacy" while enabling less

frequent dosing.

The ’338 Patent next identifies a solution: “The present inventors have surprisingly discovered that ***beneficial therapeutic effects*** can be achieved in patients suffering from angiogenic eye disorders by administering a VEGF antagonist to a patient ***at a frequency of once every 8 or more weeks***, especially when such doses are preceded by about three doses administered to the patient at a frequency of about 2 to 4 weeks.” Ex.1001, 2:3-10 (emphases added); *see also* Ex.2051, ¶¶46-53, 90-91. Thus, the ’338 Patent solved this problem by providing a treatment method that delivers a high level of efficacy but on a less frequent dosing regimen than standard-of-care ranibizumab.

## IV. CLAIM CONSTRUCTION[4]

The Board correctly recognized at institution that the preamble of Claims 1

[4] Petitioner proposes constructions for (1) “4 weeks” and “Pro re Nata (PRN)”; and (2) “VEGFR1 Component,” “VEGFR2 Component” and the “Multimerization Component.” Paper 1, 16-17. Because construction of these terms is not necessary to resolve the arguments presented by the parties, Regeneron does not propose constructions for these terms. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (providing claim construction only “to the extent necessary to resolve the controversy.”). Likewise, “initial dose” and “secondary doses” need not be construed to resolve Petitioner’s grounds. *Id*.

and 14—"A method for treating an angiogenic eye disorder in a patient"—is a positive limitation of the claims because it breathes life and meaning into the claims and provides antecedent basis for other claim terms. *See* Paper 21, 18-19 (citing Ex.1001, 1:18-20, 1:63-66, 2:23-27, 3:19-20, 5:11-13); *see also Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1340 (Fed. Cir. 2021). The Board also correctly found that the "method for treating" preamble grounds the claim in its utility. Paper 21, 19.

However, the Board's preliminary conclusion that the claimed method for treating does not require any particular level of efficacy, or for that matter, effective treatment is incorrect. Paper 21, 21. As discussed in Section IV.B.2 below, to reach this conclusion, the Board appears to have misconstrued a passage in the '338 specification to incorrectly assume that the claimed treatment methods encompass administration of non-therapeutic dose amounts. However, that incorrect assumption runs counter to the Board's findings that the "method for treating" preamble is a positive limitation and also that the claimed method requires an intent to treat an angiogenic eye disorder. Paper 21, 19; Ex.2051, ¶¶44-53.

Indeed, the intrinsic and extrinsic evidence and controlling caselaw confirm that the '338 Patent's claimed "method for treating" requires effective treatment.

### A. The Preamble Requires "Treatment," Not Just an Intent to Treat

The Board correctly found that "[a]part from the preamble, the independent claims do not elsewhere recite or indicate the usefulness of the method steps. Thus,

we agree with Patent Owner that the preamble sets forth the essence of the invention." Paper 21, 19. Thus, "treating" is "not merely the circumstance in which the method may be useful," but is instead "the *raison d'être* of the claim itself." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp*., 320 F.3d 1339, 1345 (Fed. Cir. 2003); *see* Ex.1001, Abstract, 1:18-21, 63-66, 3:19-20, 7:15-19.

Federal Circuit precedent makes clear that where a preamble is required for utility, it is a positive limitation of the claim that must be practiced to satisfy the claim. In other words, the claimed "method for treating" must actually treat, not merely intend to treat.

In *Boehringer Ingelheim*, the Federal Circuit held that the preamble's "method of growing and isolating" was a positive limitation that grounded the claim in its utility and, consequently, had to be practiced to satisfy the claim (*i.e.*, to infringe). 320 F.3d at 1345. The claim at issue recited "a method of growing and isolating swine infertility and respiratory syndrome virus," by inoculating cultured monkey cells with the PRRS virus, and incubating the inoculated cells until a cytopathic effect ("CPE") was observed. *Id*., 1343-44. The patentee argued that "isolating" and "growing" were "mere recitations of purpose" that did not "impose any limitations on the method defined by the balance of the claim." *Id*., 1345; *see* Paper 1, 17-18. The Court disagreed and found that "'growing' and 'isolating'" were needed for utility. *Boehringer*, 320 F.3d at 1345. The Federal Circuit affirmed the lower court's infringement ruling based, in part, on its finding that Schering

satisfied the "isolating" limitation each time its PRRS virus was propagated into a fresh tissue culture bottle. *Id*.

Likewise, in *Griffin v. Bertina*, the Federal Circuit affirmed the Board's finding that the preamble "method for diagnosing an increased risk of thrombosis or a genetic defect causing thrombosis" was a positive limitation and that "diagnosis is thus the essence of the invention; its appearance in the count gives life, meaning, and vitality to the claims or counts." 285 F.3d 1029, 1033 (Fed. Cir. 2002). Because Griffin did not offer evidence that he recognized the identified point mutation actually correlated with an increased risk of thrombosis (*i.e.*, satisfied the "diagnosing" limitation) before Bertina's priority date, he lost the interference. *Id.*, 1034.

*E.I. Du Pont de Nemours & Co. v. Monsanto Technology LLC,* also confirms that a preamble required for utility is a positive limitation of the claim that must be practiced. There, the Board construed a "high-throughput method for analyzing individual seeds" in the claim's preamble. IPR2014-00333, 2014 WL 3507803, *4-5 (P.T.A.B. July 11, 2014). The claim was directed to a "method for analyzing individual seeds in a population of seeds" by performing a series of steps, including sampling, testing, and analyzing seeds and their DNA. *Id*., *2. The Board concluded that the preamble was limiting (*id*., *4-5) and, on this basis, denied institution on anticipation and obviousness grounds because the prior art reference "merely disclose[d] a method that ***may be adapted***" for a high-throughput method

of analyzing seed, not one that actually performed the high-throughput method of analyzing. *See id*., *7 (emphasis added).

Thus, where a preamble is a positive limitation of the claim required for utility—*e.g.*, isolating, analyzing, or treating—courts have consistently found that the limitation must ***actually be practiced*** to satisfy the claims.

In contrast, Petitioner identifies no case where a "method for treating" is a positive limitation that requires only an intent to treat, not actually "treating," and Patent Owner is aware of none.[5] Rather, where courts have found a "method of treating" preamble to be limiting, they have consistently found that such claims require effective treatment. *See, e.g.*, *Sanofi Mature IP v. Mylan Lab'ys. Ltd.*, 757 F. App'x 988, 992-94 (Fed. Cir. 2019) (construing "a method of increasing survival" to be limiting and require increasing survival) (citing *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1332-33 (Fed. Cir. 2003)); *see also Eli Lilly*, 8 F.4th at 1340-43 (construing "method for treating" preamble as limiting because it provided the only metric for determining whether the amount administered was an

[5] Indeed, such a holding would seemingly run afoul of the mental steps doctrine—*i.e.*, an intent to treat without an efficacy requirement, merely captures the idea of treating rather than actual treatment and would therefore "lack[] patentable weight." *See Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1033, 1035 (Fed. Cir. 2018) (holding that a mental step alone is not a positive limitation).

"effective amount"); *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) (preamble directed to "method for treatment of sleep apneas" was limiting and the claims required efficacy).

Simply put, where a "method for treating" preamble is limiting, the claims require treatment, not just an intent to treat. Indeed, the purpose of the '338 Patent is to ***actually treat*** a patient with an angiogenic eye disorder by administering a VEGF antagonist in accordance with the claimed dosing regimen. Ex.2051, ¶¶16, 44, 46-53. "Treating" must be given effect to avoid rendering the claim a mere "academic exercise." *See Boehringer*, 320 F.3d at 1345.

### B. The Claimed Treatment Method Requires a High Level of Efficacy That Is Not Inferior to the Existing Standard-Of-Care

As discussed above, by the filing of the '338 Patent, a highly effective anti-VEGF therapy had already been approved for treating angiogenic eye disorders, namely ranibizumab (Lucentis). It is undisputed that after Lucentis' approval in 2006, the standard-of-care evolved, and it was no longer considered treatment to allow patients to lose vision. Ex.2051, ¶¶17, 54-68, 73; Ex.2130 (Albini Tr.), 149:5-151:4, 153:2-6 (Lucentis and off-label Avastin as standard of care), 155:10-17 (Macugen not considered effective treatment by 2011). Rather, Lucentis moved the goal post and ***visual acuity gains*** became the new standard-of-care in treating wAMD, while older therapies, like Macugen, became "ancient history." Ex.2051, ¶¶17, 54-68; Ex.2050, ¶¶40-52, 101; Ex.2130 (Albini Tr.), 149:17-22 ("I think also they included [the ranibizumab] arm [in the VIEW trials]

because the FDA would have required them to treat patients that were in the study with the standard of care."); *see also id*., 153:2-6, 28:14-29:3. In fact, clinical trials conducted after Lucentis' approval, including those described in the '338 Patent, typically measured efficacy in terms of visual acuity gains, not losses.[6] Ex.2051, ¶¶71-72; Ex.2050, ¶¶43-44. Even so, there remained a need in the art to reduce the burden of frequent injections and monitoring visits while maintaining the high level of efficacy that the retina community came to expect with ranibizumab and off-label Avastin. See *supra* Section II. This was the precise problem that the '338 Patent set out to solve. Ex.2051, ¶51, Ex.2050, ¶¶156-159. Both the intrinsic and extrinsic evidence confirm that the claimed method for treating requires treatment of a patient with a high level of efficacy, on par with the prevailing standard-of-care at the time of filing. Ex.2051 ¶¶54-84.

### 1. The '338 Patent Confirms That the Claimed Treatment Method Requires a High Level of Efficacy

The *sine qua non* of the '338 Patent was to find a treatment method that maintained the "high level of efficacy" of standard-of-care ranibizumab while enabling less frequent dosing. Ex.1001, 1:49-59. The '338 Patent notes that, "[o]ne advantage of such a dosing regimen is that, for most of the course of treatment (i.e.,

[6] As discussed below, Regeneron used proportion of patients losing ≤15 letters on ETDRS as a primary endpoint for its VIEW trials because Lucentis was an active control and Lucentis was approved on the basis of that endpoint.

the tertiary doses), it allows for less frequent dosing (e.g., once every 8 weeks) compared to prior administration regimens for angiogenic eye disorders which require monthly administrations throughout the entire course of treatment. (*See, e.g.*, prescribing information for Lucentis® [ranibizumab], Genentech, Inc.)." Ex.1001, 2:15-22.

To accomplish this, Regeneron conducted two Phase III studies in wAMD, which are described in Example 4 of the '338 Patent. Ex.2051, ¶¶74-80; Ex.2050 ¶¶75-83. "The primary objective of these studies was to assess the efficacy of IVT [intravitreally] administered VEGFT compared to ranibizumab (Lucentis, Genentech, Inc.) in a non-inferiority paradigm." Ex.1001, 9:21-25; *see also* Ex.2130 (Albini Tr.), 170:14-22. A non-inferiority study design using ranibizumab as the active control was selected for both ethical and practical reasons. Ex.2130 (Albini Tr.), 149:5-151:4; Ex.2051, ¶¶77-78, 82; Ex.2050, ¶¶75-78; Ex.2097, 7. The primary endpoint of loss of ≤15 letters on ETDRS was selected to maintain constancy with the primary endpoint in Lucentis' pivotal trials. Ex.2050, ¶¶76-78; Ex.2051 ¶¶76-78; Ex.2097, 8, 12.

Table 1 summarizes the results of Regeneron's Phase III studies and shows that a similar proportion of subjects in each of the VEGF Trap-Eye dosing arms, including the Q8 dosing arm, met the primary endpoint of loss of ≤15 letters on ETDRS (95.1% or 95.6%) as compared to monthly ranibizumab (94.4%). Table 1 also reports similar mean improvement in vision as compared to monthly

ranibizumab, with an average gain of 7 or more letters for the Q8 dosing regimen:

TABLE 1

| | Ranibizumab 0.5 mg monthly (RQ4) | VEGFT 0.5 mg monthly (0.5Q4) | VEGFT 2 mg monthly (2Q4) | VEGFT 2 mg every 8 weeks[a] (2Q8) |
|---|---|---|---|---|
| Maintenance of vision* (% patients losing <15 letters) at week 52 versus baseline | | | | |
| Study 1 | 94.4% | 95.9%** | 95.1%** | 95.1%** |
| Study 2 | 94.4% | 96.3%** | 95.6%** | 95.6%** |
| Mean improvement in vision* (letters) at 52 weeks versus baseline (p-value vs RQ4)*** | | | | |
| Study 1 | 8.1 | 6.9 (NS) | 10.9 ($p < 0.01$) | 7.9 (NS) |
| Study 2 | 9.4 | 9.7 (NS) | 7.6 (NS) | 8.9 (NS |

[a]Following three initial monthly doses

*Visual acuity was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.
**Statistically non-inferior based on a non-inferiority margin of 10%, using confidence interval approach (95.1% and 95% for Study 1 and Study 2, respectively)
***Test for superiority
NS = non-significant

Ex.1001, 14:3-23 (annotated with highlighting). The POSA[7] would have concluded from these data that VEGF Trap-Eye, including on a Q8 dosing schedule, achieved and maintained a high level of efficacy that was non-inferior to standard-of-care Lucentis. Ex.2130 (Albini Tr.), 172:20-173:18; Ex.2051, ¶¶79-80; Ex.2050 ¶¶80-84.

[7] Regeneron disagrees with Petitioner's definition of the POSA. Pet. 22. For purposes of the '338 Patent, the POSA is an ophthalmologist with experience in treating angiogenic eye disorders, including through the use of VEGF antagonists. Ex2051, ¶28. However, Regeneron does not believe that parties differing definitions of "the POSA" matter for any argument in this Patent Owner Response.

The prosecution history confirms that the claimed treatment methods must achieve a high level of efficacy. During prosecution, Regeneron relied on Heier 2012 (Ex.1018) to overcome a double patenting rejection by arguing that the "treatment protocol" encompassed by the claimed invention resulted in surprising efficacy, ***i.e., noninferiority to ranibizumab***, despite less frequent dosing than the standard of care (*i.e.*, monthly dosing of ranibizumab). Ex.1017, 288-91, 315; *id*., 290 ("[T]he finding that remarkably similar improvement in vision and anatomic measures can be achieved with less than monthly intravitreal aflibercept injections and without requiring monthly monitoring visits provides an important advance for both patients and their treating physicians."). Regeneron explained that a "treatment protocol" with less frequent, tertiary dosing "once every 8 weeks" was surprisingly efficacious, which ultimately resulted in the issuance of the Challenged Claims.[8] *See id*., 289; *Fenner Invs., Ltd. v. Cellco P'ship*, 778 F.3d 1320, 1323

[8] Petitioner relies on *Purdue* and *Mylan* to argue that Regeneron "is foreclosed … from arguing that its reliance on alleged 'unexpected results' during prosecution demonstrates that efficacy is a necessary feature of the claimed method." Paper 1, 18. But *Purdue* relates to prosecution history estoppel, which is not at issue here. Moreover, *Mylan* is distinguishable because the Board's conclusion that prosecution history statements did not support construing the preamble as limiting was based on the fact that the disputed term was not discussed during prosecution. But here,

(Fed. Cir. 2015).

Moreover, the POSA would have understood that a less frequent dosing regimen that was inferior to the standard-of-care, or worse yet—ineffective—would not have been viewed as treatment by 2011. Macugen presents a case-in-point. Macugen was approved with a recommended dosing schedule of ***once every 6 weeks***, as compared to Lucentis' recommended dosing schedule of ***once every 4 weeks***. Ex.2038 (Macugen label), 6-7. Macugen demonstrated some level of efficacy in that it slowed vision loss compared to sham control. *Id*.; Ex.2050, ¶30; Ex.2051 ¶¶57, 73. However, once Lucentis was approved and showed that it could restore vision, no one considered Macugen to be effective treatment and practitioners stopped using it, even though it was indicated for less frequent dosing. Ex.2130 (Albini Tr.), 155:10-17; Ex.2038; Ex.2050, ¶42; Ex.2051, ¶¶54-57, 65-68, 73. Thus, by 2011, the POSA would not have considered an extended dosing regimen that was inferior to the standard-of-care to be an effective treatment. Indeed, such a treatment would not have been used by clinicians by 2011. Ex.2130 (Albini Tr.), 149:5-151:4; Ex.2050, ¶¶52, 83. Thus, the POSA would have understood what the '338 Patent makes explicit—that the claimed "method for treating" must provide highly effective treatment (non-inferior to the standard-of-

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Regeneron's discussion of unexpected results during prosecution was unequivocally related to the "treat[ment]" limitation.

care at the time of patent filing) to the patient. Ex. 2051 ¶¶46-84.

### 2. The Claimed Treatment Method Does Not Encompass Non-Therapeutic Dose Amounts

In initially finding that the "method for treating" limitation does not require efficacy, the Board relied on a single specification passage that states: "The amount of VEGF antagonist administered to the patient in each dose is, in most cases, a therapeutically effective amount." Paper 21, 20 (citing Ex.1001, 6:48-50). Based on the phrase "in most cases," the Board concluded that, in some cases, the invention does not require dosing a therapeutically effective amount and, consequently, the "claims do not require the recited method steps to provide an effective treatment." Paper 21, 20. The Board's preliminary interpretation of this specification passage and its conclusion are incorrect.[9]

Rather, the Column 6 passage merely observes that "[t]he amount of VEGF antagonist administered to the patient" is an amount that is "therapeutically effective" "in most cases"—*i.e.*, even if some patients do not respond. This is consistent with the data reported in the '338 specification and with the knowledge in the art. Ex.2051, ¶¶49-53; Ex.2130 (Albini Tr.), 192:20-193:7 (efficacy on a

[9] The Board's determination that practicing the method does not require "any particular level of effectiveness" (Paper 1, 20) and thus includes no effectiveness at all (*i.e.*, an ineffective method) is inconsistent with its determination that practicing the claims requires an intent to treat.

population basis), 200:15-19 ("so even if a certain treatment paradigm is shown to be on average effective … they're not going to work for every—for every single instance."). For example, in the clinical trial data reported in Example 4, VEGF Trap-Eye demonstrated that about 96% of subjects achieved the "primary endpoint (prevention of moderate or severe vision loss as defined above)." Ex.1001, 12:66-13:23. Even so, the remaining ~4% of study subjects failed to meet this endpoint. *Id.*; Ex.2051, ¶50. The VEGF Trap-Eye treatment, therefore, was "therapeutically effective" "in most cases" but may not have been in a small remainder of cases. That does not mean that the claims encompass ineffective treatment methods, such as the administration of non-therapeutically effective dose amounts, as the Board appears to hold.

The Column 6 passage should not be read in isolation and did not redefine the invention to include methods that are not therapeutically effective.[10] Such

[10] As an initial matter, it is the claim, not the specification, that defines the invention. Even if the Column 6 passage could be read to encompass non-therapeutic dose amounts, it does not follow that such ineffective amounts would be encompassed by a claim directed to a treatment method. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 957 (Fed. Cir. 1983) ("That claims are interpreted in light of the specification does not mean that everything expressed in the specification must be read into all the claims. … The claim, not the specification, measures the invention.").

methods would not be "treatment" as that term is understood by the POSA. Ex.2051, ¶¶47-53. Indeed, both parties' experts agree that by 2011, it would not have been ethical to knowingly administer an ineffective dose amount to a study subject because highly effective treatment options were available in the art. Ex.2130 (Albini Tr.), 148:17-151:4; Ex.2051, ¶¶77-78; Ex.2050 ¶77. As the Board correctly observed, "the Specification repeatedly characterizes the method as one that is useful for treating angiogenic eye disorders in patients." Paper 21, 19; *see also Budde v. Harley-Davidson, Inc.*, 250 F.3d 1369, 1379-80 (Fed. Cir. 2001) ("In construing terms used in patent claims, it is necessary to consider the specification as a whole, and to read all portions of the written description, if possible, in a manner that renders the patent internally consistent."). Accordingly, the claimed treatment methods require administering a therapeutically effective dose amount.

### C. Mylan's Proposed Construction of "Method for Treating" Is Inconsistent with the State of the Art and the '338 Patent's Intrinsic Record

Mylan acknowledges that there is no express definition of "treating" in the '338 Patent and, further, that the term "efficacy" cannot be equated with "treating." Paper 1, 21; Ex.2130 (Albini Tr.), 157:18-159:21; 186:5-187:2, 189:13-190:3; 201:8-202:2. Nonetheless, Mylan contends that the '338 Patent only requires that "the patient exhibit a loss of fifteen or fewer letters on the Early Treatment Diabetic Retinopathy Study ("ETDRS") visual acuity chart within 104 weeks of treatment

initiation." Paper 1, 21 (citing Ex.1001, 7:15-32). Mylan's proposed construction ignores the state of the art in 2011, misconstrues the '338 specification, and is undermined by the admissions of its own expert.

First, Mylan improperly relies on a single sentence in Column 7 to argue for an extremely low level of efficacy. But Column 7 refers to clinical trial endpoints that were used to measure or assess results, not to define an outcome that reflects an effective treatment method. The POSA would have understood that loss of ≤15 letters on ETDRS (Ex.1001, 7:24-29), or a gain of letters on ETDRS (*id*., 7:29-32), correspond to common clinical trial endpoints used to measure results of angiogenic eye disorder treatments in the art, and in the '338 Patent specification. Ex.2130 (Albini Tr.), 181:11-22; Ex.2051, ¶70. Moreover, the POSA would have understood that the '338 Patent discloses a number of different clinical trial endpoints to measure results, most of which measure ***visual acuity gains***. Ex.2051, ¶¶70, 72-73.

Mylan cherry-picks one clinical trial endpoint (loss of ≤15 letters on ETDRS) and ignores other endpoints (including ***visual acuity gains***) that were used to measure results in the '338 Patent. Ex.1001, 7:29-32, 8:34-41, 9:37-44, 14:52-54. But it is undisputed that the POSA ***would not have considered*** loss of ≤15 letters on ETDRS to reflect an effective method for treating an angiogenic eye disorder by 2011. Ex.2130 (Albini Tr.), 193:19-194:15; Ex.2051, ¶¶73, 82-84; Ex.2050, ¶¶42, 83.

Mylan also ignores the context for the "loss of ≤15 letters on ETDRS" clinical trial endpoint in the '338 Patent. This endpoint was used to measure non-inferiority of treatment with VEGF Trap-Eye to ranibizumab, as described in Example 4. The POSA reviewing the '338 Patent would have understood that to show non-inferiority in the clinical trial, it was not enough that some subjects met this "loss of ≤15 letters on ETDRS" endpoint. Rather, Regeneron needed to demonstrate that a similar proportion of subjects met this endpoint as compared with ranibizumab (*i.e.*, 95% of VEGF Trap-Eye subjects as compared to 94% of ranibizumab subjects). Ex.1001, 13:18-21; Ex.2130 (Albini Tr.), 171:14-172:16; Ex.2051, ¶82; Ex.2050, ¶83; Ex.1018, 2040. Taken together with the other data presented in the '338 Patent (including visual acuity gains), the POSA would have understood that VEGF Trap-Eye was highly effective (non-inferior to Lucentis), even when dosed Q8. Ex.2051, ¶¶79-80, 82-84; Ex.2130 (Albini Tr.), 171:14-173:18. The POSA would not have read Column 7 out of context and ignored the state of the art at the time of filing. *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1347 (Fed. Cir. 2020) (reversing claim construction based solely on one statement in the specification).

### D. The "Tertiary Dose" Limitation Requires Maintaining a High Level of Efficacy Throughout the Course of Treatment

The claim term "tertiary dose(s)" means "dose(s), administered after the initial and secondary doses, that ***maintain(s) the efficacy gain*** achieved after the initial and secondary doses." This follows from the intrinsic record.

The parties' experts agree that "tertiary dose" does not have a "previous meaning to those of ordinary skill in the art," (Ex.2001, ¶43; Ex.1002, ¶41), "apart from the patent." *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300 (Fed. Cir. 2004). They also agree that "tertiary dose(s)" occur after secondary doses. Ex.1001, 3:31-38; Paper 21, 22-23. This, however, does not provide a complete definition of "tertiary dose" because it says nothing about the size or purpose of the tertiary dose. Accordingly, the Board must look to the specification as a whole to supply this missing information. *See Abraxis Biosci., Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1376-77 (Fed. Cir. 2006).

Contrary to Mylan's suggestion, the specification does not expressly define "tertiary dose." When a patent owner uses an unmistakable format to define certain terms but not others, a court will not presume those other terms have been formally defined by the inventor. *See, e.g.*, *Meds. Co. v. Mylan, Inc.*, 853 F.3d 1296, 1300, 1306 (Fed. Cir. 2017) (specification using an unmistakable format to define certain terms but not others). Here, Regeneron used the specific "linguistic format"—"as used herein"—to define some terms. *See, e.g.*, Ex.1001, 3:18-21, 3:32-36, 5:23-26. Regeneron, however, did not use this format to describe a "tertiary dose." *See, e.g.*, Ex.1001, 3:42-44. Consequently, the '338 Patent's "entire specification" and prosecution history confirm Regeneron's construction that includes both the order and purpose of the "tertiary dose"—namely, "dose(s), administered after the initial and secondary doses, that ***maintain(s) the efficacy gain*** achieved after the initial

and secondary doses." *See supra* Sections III, IV.B.1.

The temporal sequence of administration, by itself, does not say anything else about the dose. *See Baxalta Inc*., 972 F.3d at 1347 (reversing claim construction based solely on one statement in the specification). Accordingly, if "tertiary dose" were defined based only on its temporal sequence, the Challenged Claims would encompass administering ineffective doses of the recited antagonist—*e.g.*, infinitesimal quantities that are not capable of achieving any efficacy. This would be an incongruous interpretation of claims directed to a "method for treating" angiogenic eye disorders.

## V. GROUNDS 1, 3-5: PETITIONER FAILS TO DEMONSTRATE THAT "VEGF TRAP-EYE" WAS KNOWN IN THE ART TO CORRESPOND TO SEQ ID NO:1

It is undisputed that VEGF Trap-Eye was not publicly available before EYLEA's FDA approval on November 18, 2011. Ex.2130 (Albini Tr.), 319:16-320:9. Regeneron's clinical trials involving VEGF Trap-Eye were conducted under strict confidentiality, as was Regeneron's submission of information to FDA regarding VEGF Trap-Eye pre-approval.[11] Thus, the POSA would not have had

[11] Regeneron required its clinical investigators to sign confidentiality agreements that restricted disclosure of information regarding VEGF Trap-Eye. Ex.2050, ¶¶70-72; Ex.2051, ¶¶171-172. Likewise, all information concerning VEGF Trap-Eye

access to the amino acid or nucleic acid sequence of VEGF Trap-Eye before the priority filing date of the '338 Patent. Anticipation requires "each and every claim limitation [be] found either expressly or inherently in a single prior art reference." *King Pharms. Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1274 (Fed. Cir. 2010) (quotations omitted). Because none of Dixon (Ground 1), Regeneron (8-May-2008) (Ground 3), NCT-795 (Ground 4) or NCT-377 (Ground 5) discloses—either expressly or inherently—the amino acid or nucleic acid sequence of VEGF Trap-Eye, none of these references anticipates the Challenged Claims.

### A. Petitioner's Grounds 1, 3-5 References Do Not Expressly Disclose the Amino Acid or Nucleic Acid Sequence of VEGF Trap-Eye

It is undisputed that Petitioner's references do not disclose sequence information for "VEGF Trap-Eye." *See* Ex.2129 (Gerritsen Tr.), 33:10-34:2; 103:23-104:18; 109:15-110:3 (agreeing that the amino acid sequence of VEGF Trap-Eye is not disclosed in Dixon, Regeneron (8-May-2008), NCT-795, or NCT-377); Ex.2130 (Albini Tr.), 341:13-16; *see also* Ex.2049 (Klibanov Decl.), Section IX; Ex.2048 (Del Priore Decl.), Section X. Consequently, Petitioner must show inherent anticipation of the amino acid and nucleic acid limitations of claims 1 and 14, respectively. For the reasons detailed below, Petitioner has failed to establish

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submitted to FDA was maintained as confidential pre-approval. *See* 21 CFR §§ 601.50, 601.51.

inherent anticipation because the POSA would not have necessarily known or determined that "VEGF Trap-Eye" had the claimed amino acid or nucleic acid sequence based on public information available as of priority filing date of the '338 Patent.

### B. Petitioner's Grounds 1, 3-5 References Do Not Inherently Disclose the Amino Acid or Nucleic Acid Sequence of VEGF Trap-Eye

In the absence of express disclosure, Petitioner asserts that its Grounds 1 and 3-5 references inherently disclose the amino acid and nucleic acid sequences of VEGF Trap-Eye. However, "[i]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (citing *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). Rather, to succeed on inherency, Petitioner must establish that the amino acid or nucleic acid sequence of VEGF Trap-Eye "is necessarily present" in the Ground 1, 3-5 references. *Continental Can Co. USA v. Monsanto*, 948 F.2d 1264, 1268 (Fed. Cir. 1991); *see also Rexnord Indus., LLC v. Kappos*, 705 F.3d 1347, 1355 (Fed. Cir. 2013) ("[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that ***must necessarily*** include the unstated limitation.") (emphasis added).

The Federal Circuit has also instructed that inherency cannot be invoked where there is incomplete disclosure of a composition in the prior art—*e.g.*, VEGF

Trap-Eye—because "incomplete description of the [claimed] composition elements denied skilled artisans from having access to that composition." *See Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018) (clinical studies of a testosterone supplement ("TU") did not inherently disclose the composition because it was not reported and thus unknown to a skilled artisan years after the priority date). Similarly, in *Amgen, Inc. v. Alexion Pharms.*, the Board rejected an inherent anticipation argument based on the assertion that a prior art reference's disclosure of the name "eculizumab" inherently disclosed the claimed protein. IPR2019-00741, Paper 15, 20 (P.T.A.B. Aug. 30, 2019). Because the Board found that the term "eculizumab" referred to at least two different proteins in the prior art, including the unclaimed "Thomas IgG4 isotype eculizumab," the prior art "would not have necessarily led the skilled artisan to the claimed antibody," there was no inherent anticipation. *Id*., 24-25.

As in *Endo* and *Amgen*, Petitioner's references here do not adequately disclose the amino acid or nucleic acid sequence of VEGF Trap-Eye such that the POSA would have known that it necessarily corresponded to the claimed sequences. Petitioner's cited references do not identify the amino acid or nucleic acid sequences of "VEGF Trap-Eye," nor do they show that "VEGF Trap-Eye" must have had the recited sequences of the Challenged Claims. Consequently, Petitioner's references do not anticipate the Challenged Claims.

### 1. Dixon Does Not Disclose That VEGF Trap-Eye Shares the Same Amino Acid Sequence of Aflibercept

Petitioner relies heavily on Dixon's statement that "VEGF Trap-Eye" and aflibercept (the oncology product) share a "molecular structure" to show inherency of the VEGF Trap-Eye amino acid sequence. Ex.1006, 1575. Dixon, however, does not state that "VEGF Trap-Eye" and aflibercept have the same amino acid sequence, and a shared "molecular structure" does not necessarily evidence an identical amino acid sequence. It is well-established that protein molecules, like VEGF Trap-Eye, have multiple levels of "structure," including primary, secondary, tertiary, and quaternary structures. Ex.2049, ¶¶50-56 (citing Ex.2010, 4); Ex.2048, ¶¶66-72. The term "molecular structure" was repeatedly used in the literature to refer to the three-dimensional structure of the protein, rather than a protein's amino acid sequence. Ex.2049, ¶¶57-63 (citing Ex.2067, 1449 ("This study was designed to disclose the ***molecular structure*** of tau" proteins that have rodlike three-dimensional structure.) (emphasis added).

Importantly, the POSA would have known that proteins with different amino acid sequences may have the same molecular structure or *vice versa*. Ex.2049, ¶¶61-63 (citing Ex.2076 at 1292) (noting that thioesterases can have "very different primary structures but common tertiary structures"); *id.*, ¶58 (citing Ex.2069, 1019, 1026) (noting that over 1000 pairs of proteins with similar molecular structures but ***dissimilar*** amino acid sequences have been cataloged); *id*., ¶59 (citing Ex.2070, 41) (murine and bovine antibody domains have "***surprisingly similar structures*** and

stabilities, ***considering the marginal sequence conservation*** between the two molecules."); *id*., ¶63 ("[A] protein with a given amino acid sequence expressed in *E. coli* may have a different overall structure when it is expressed in a mammalian host cell."); *see also* Ex.2048, ¶¶68-69.

Moreover, Dixon itself suggests that the "molecular structure" of VEGF Trap-Eye refers to a more general selection and arrangement of receptor binding domains and an Fc region, not a precise amino acid or nucleic acid sequence. Ex.2049, ¶¶65-66; Ex.2048, ¶¶71-72; Ex.2130 (Albini Tr.), 337:17-21 ("Dixon is describing the structure of VEGF Trap-Eye by its key binding domains in the Fc region [in Fig. 1]. A. That's correct."). Specifically, Dixon uses the term "molecular structure" right after explaining that: "***Structurally***, VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment (Fig. 1)." Ex.1006, 3, Fig. 1. Figure 1 shows a stylized version of VEGF receptors 1 and 2 and the binding domains that lead to the creation of a VEGF Trap molecule Ex.1006, 1576.

Simply put, the POSA would have understood that Dixon's statements concerning the "molecular structure" of VEGF Trap-Eye could have referred to the protein's three dimensional (3D) structure, or overall configuration of VEGF binding domains, rather than its primary structure (*i.e.*, amino acid sequence). Ex.2049, ¶¶49-66; Ex.2048, ¶¶66-72. Petitioner's experts agree with this understanding. Ex.2129 (Gerritsen Tr.), 73:25-74:4 ("[T]he protein's ***molecular***

***structure*** will refer to its secondary structure, correct? A. … I think that it would refer to the structural information. That's what it says, 'structure.'") (emphasis added); Ex.2130 (Albini Tr.), 107:16-22 (agreeing that when he refers to structural changes in a protein he is "referring to changes in the 3D structure of the protein.").

### 2. The POSA Would Have Reason to Doubt That VEGF Trap-Eye Corresponded to Only Aflibercept

#### a. The POSA could have concluded that VEGF Trap-Eye was a genus of proteins with different amino acid sequences

The structural information that Dixon provides for VEGF Trap-Eye—"a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment"—was insufficient to distinguish VEGF Trap-Eye from any other protein comprising a VEGFR1 domain 2, VEGFR2 domain 3, and a human Fc region. Rather, the POSA would have understood Dixon's description to correspond to a genus of protein sequences reported in the art, an understanding which would have been confirmed by variability in the reported molecular weights of "VEGF Trap-Eye." Ex.2049, ¶¶67-83.

Regeneron developed, tested, and published on a variety of engineered VEGF fusion proteins it called "VEGF Trap" molecules, only some of which included both VEGFR1 and VEGFR2 binding domains. Ex.2049, ¶68-75 (citing Ex.1004, 11394). Even the term "VEGF TrapR1R2," which is a subset of VEGF Trap proteins, was known to encompass a genus of protein sequences, any one of which could satisfy Dixon's structural definition, but would not necessarily possess the

amino acid sequence of the Challenged Claims. Ex.2049, ¶¶68-75 (identifying multiple VEGF TrapR1R2 proteins with different amino acid sequences). Indeed, each of the references on which Petitioner relies includes multiple VEGF-Trap sequences, including multiple VEGF-TrapR1R2 sequences.

**b. The prior art reported VEGF Trap-Eye to have different molecular weights than aflibercept**

In addition to the genus of published protein sequences falling within the description of "VEGF Trap-Eye," the POSA would have been aware of different reported molecular weights for "VEGF Trap-Eye." For example, the prior art reports that "VEGF Trap-Eye[24] is a ***110-kDa*** recombinant protein," and that "VEGF Trap-Eye (Regeneron Inc.) is a ***115-kDa*** recombinant fusion protein." Ex.2049, ¶¶76-78 (citing Ex.1075, 403); *see also* Ex.2048, ¶¶87-91. In contrast, the molecular weight of aflibercept was routinely reported as 115 kDa. Ex.2049, ¶77 (citing Ex.2014, 596 and Ex.2015, [0010]); *see also* Ex.2048, ¶88.

The POSA would have recognized that reported differences in molecular weights among VEGF Trap-Eye proteins, as well as those between the reported molecular weights of VEGF Trap-Eye and aflibercept, could reflect differences in the amino acid sequence. Ex.2049, ¶78; Ex.2048, ¶¶89-91. These differences in reported molecular weights of "VEGF Trap-Eye," coupled with Dixon's generic description of "VEGF Trap-Eye" as having binding domains from human VEGFR1 and human VEGFR2 with a human IgG Fc, would support the conclusion that "VEGF Trap-Eye" referred to a genus of protein sequences that was not limited to

the claimed amino acid sequence. Ex.2049, ¶¶67-83; Ex.2048, ¶¶90-91. Moreover, equating aflibercept with "VEGF Trap," "VEGF Trap-Eye," and "VEGF-Trap$_{R1R2}$,"[12] would not have suggested to the POSA that "VEGF Trap-Eye" corresponded to ***only*** aflibercept, but rather, may have suggested that "VEGF Trap-Eye," like "VEGF Trap" or "VEGF-Trap$_{R1R2}$," describes multiple different protein sequences. Ex.2049, ¶80.

In view of this conflicting prior art, Petitioner fails to establish that the term "VEGF Trap-Eye" was known to necessarily refer to aflibercept, and to comprise the amino acid or nucleic acid sequence recited in the Challenged Claims.

**c. None of Petitioner's references discloses that "VEGF Trap Eye" corresponds to only the recited sequence**

Petitioner and Dr. Albini rely on various Regeneron patents and published applications[13]—the '173 Patent (Ex.1008), '758 Patent (Ex.1010), '757 Patent

[12] Paper 1, 23 ("Aflibercept, VEGF Trap, VEGF Trap-Eye, VEGF-Trap$_{R1R2,}$ and AVE0005 are simply different names for the same molecule.") (citing Ex.1007).

[13] As discussed in the POPR, Petitioner also relies on Regeneron's PTE Application (Ex.1024), filed nearly a year after the priority date, to try to connect "VEGF Trap-Eye" to "aflibercept" (Paper 1, 24), but the meaning of "VEGF Trap-Eye" must be understood as the POSA would have viewed the term as of the priority date without reference to how the meaning of the term may have later changed. *See Schering*

(Ex.1022), '959 Patent (Ex.1023), and Dix published patent application (Ex.1033)—to purportedly show correspondence between the recited VEGF antagonist fusion protein and amino acid sequences and sequences disclosed in the art. Paper 1, 24 & n.6. The trouble with Petitioner's hindsight approach is that none of its cited patents identifies any of its disclosed sequences as "VEGF Trap-Eye" (or "aflibercept" for that matter), and other VEGF Trap sequences, including other VEGF-Trap$_{R1R2}$ sequences, were known in the art and published in some of these same references. Ex.2049, ¶¶69-74, 84-89; Ex.2130 (Albini Tr.), 325:21-326:17 (agreeing that no prior art Regeneron patent discloses the amino acid or nucleic acid sequence for "VEGF Trap-Eye"). Thus, disclosure of the recited sequences among other disclosed sequences in Petitioner's cited references would not have informed the POSA that VEGF Trap-Eye necessarily possessed the amino acid sequence or nucleic acid sequence of the Challenged Claims.

**d. Regeneron consistently characterized "VEGF Trap-Eye" as an ophthalmology product and "aflibercept" as an oncology drug**

Regeneron's publications (and Dixon), consistently refer to Regeneron's ophthalmology drug as "VEGF Trap-Eye," and refer to Regeneron's oncology

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*Corp. v. Amgen Inc.*, 222 F.3d 1347, 1354 (Fed. Cir. 2000) (holding a term is to be understood based on knowledge in the art as of the priority date, even if it later acquires a different meaning).

product as aflibercept. Ex.2048, ¶¶73-79 (showing consistent use of the term VEGF Trap-Eye for ophthalmology and aflibercept for oncology in clinical trial submissions, press releases, SEC filings, and scientific publications). Indeed, Dr. Albini, Petitioner's expert, acknowledged that Regeneron consistently referred to VEGF Trap-Eye and aflibercept for different therapeutic indications and that it was "certainly possible" that the POSA reading Dixon could have concluded that VEGF Trap-Eye and aflibercept were different products. Ex.2130 (Albini Tr.), 334:20-335:9, 342:12-343:4. This is fatal to Petitioner's inherency assertion.

Relatedly, the POSA would have known that Genentech's anti-VEGF oncology drug (Avastin) had a different protein sequence than its anti-VEGF ophthalmology drug (Lucentis), even though Avastin was used off-label in ophthalmology. Ex.2048, ¶¶82-85; *see also* Ex.2130 (Albini Tr.), 342:5-11. Specifically, the POSA would have known that Genentech modified its anti-VEGF oncology drug's protein sequence to make it more compatible for ophthalmic administration. Ex.2048, ¶¶83-85. Thus, it would have been reasonable for the POSA to conclude that Regeneron's anti-VEGF oncology product, aflibercept, was different in sequence from its ophthalmology product, "VEGF Trap-Eye." Ex.2048, ¶86.

The mere possibility that "VEGF Trap-Eye" could include the recited amino acid or nucleic acid sequence is insufficient to demonstrate inherency for anticipation. *See Endo*, 894 F.3d at 1383; *see also In re Oelrich*, 666 F.2d at 581.

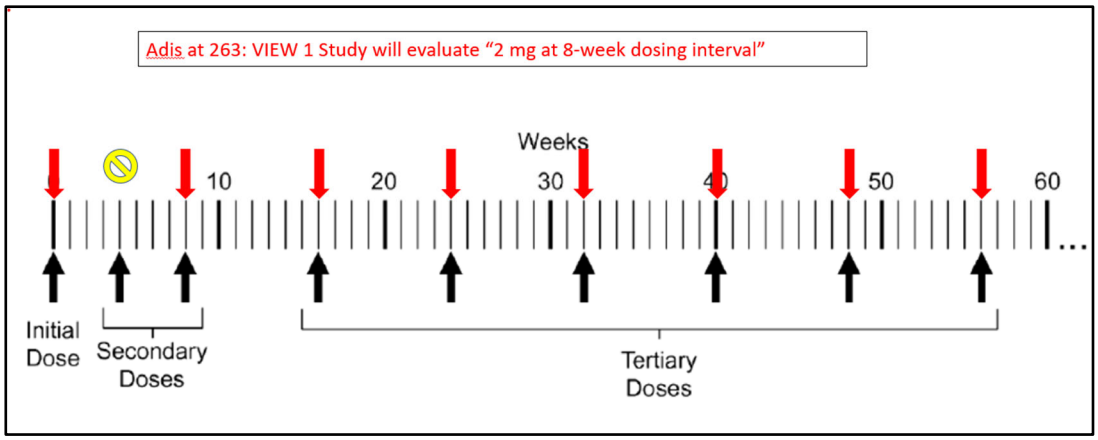
Instead, each of Petitioner's references provide an "incomplete description" of VEGF Trap-Eye, thereby "den[ying] skilled artisans from having access to" that claimed invention. 894 F.3d at 1383. Thus, Petitioner has failed to establish that any of its Ground 1 and 3-5 references necessarily discloses the amino acid or nucleic acid sequence of VEGF Trap-Eye. *AstraZeneca LP v. Apotex*, 633 F.3d 1042 (Fed. Cir. 2010).

## VI. GROUND 2: ADIS DOES NOT ANTICIPATE THE CHALLENGED CLAIMS

To anticipate, a reference "must not only disclose all elements of the claims within the four corners of the document, but must also disclose those elements arranged as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (internal quotations omitted). Adis provides incomplete and inconsistent information that would not have clearly disclosed to the POSA the dosing regimen set forth in the Challenged Claims.

Petitioner relies on two passages in Adis, regarding the prospective VIEW1/2 trials, as disclosing the claimed dosing regimen. Paper 1, 45-46. Petitioner points to the statement that VIEW 1 "will evaluate the safety and efficacy of intravitreal aflibercept at doses of 0.5 mg and 2.0 mg administered at 4-week dosing intervals, and ***2.0 mg at an 8-week dosing interval***, compared with 0.5 mg ranibizumab administered every 4 weeks." Ex.1007, 263 (emphasis added). Petitioner's expert, Dr. Albini, agrees that this passage does ***not*** disclose the claimed dosing regimen. *See* Ex.2130 (Albini Tr.), 304:11-22 ("I think it would be reading into it to assume

anything about loading doses. There's no mention of loading doses."). A diagram of Adis's disclosure of VIEW 1 is depicted below:




Ex.2132; Ex.2130 (Albini Tr.), 297:21-298:4 ("[Y]ou'll agree that it's missing a 2-milligram dose at week 4; correct? … A. That's correct."). Adis's description of VIEW 1 as testing 4-week and 8-week dosing intervals is consistent with other descriptions of Regeneron's VIEW trials in the art. Ex.1012, 2 (4/28/2008 press release) (describing Phase 3 trials as "evaluating VEGF Trap-Eye using four- and eight-week dosing intervals…."); Ex.1041, 1 (2/26/2009 press release) ("The VIEW 1 and VIEW 2 trials are both evaluating dosing intervals of four and eight weeks for VEGF Trap-Eye compared with ranibizumab dosed according to its U.S. label every four weeks over a year."); Ex.1054, 1 (8/7/2007 press release); Ex.1067, 4.

Petitioner next points to Adis's disclosure regarding VIEW 2: "This study will evaluate the safety and efficacy of aflibercept at 0.5 mg and 2.0 mg administered at 4-week intervals and 2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." Ex.1007, 263. Adis's description of

VIEW 2 is incomplete and ambiguous in that it fails to identify which of the three study arms, if any, actually receives the "one additional 2.0 mg does at week 4." Moreover, Adis reports that VIEW 1 tests different dosing regimens than VIEW 2 tests (regardless of which arm receives the additional 2.0 mg dose at week 4), which is inconsistent with other publications, including from Regeneron, describing the trials as testing "identical" dosing regimens. Ex.2080, 4 ("Two identical, noninferiority Phase 3 studies called VIEW 1 and VIEW 2…are currently under way to examine the effects of VEGF Trap-Eye in wet AMD."); Exs.1014, 1015. The POSA would have had reason to doubt the accuracy of Adis's description of the VIEW trials in light of Adis's incomplete and inconsistent information as compared to other reports regarding the VIEW trials, including from more authoritative sources, in the art. Ex.2049, ¶¶42-43; Ex.2048, ¶¶50-53; Exs.1014, 1015; Ex.2080.

Petitioner and its expert use improper hindsight to interpret Adis's disclosure of VIEW 1 and 2 to arrive at the claimed regimen. *Janssen Pharms., Inc. v. Watson Lab'ys, Inc.*, C.A. No. 08-5103(SRC), 2012 WL 3990221, *6-10 (D.N.J. Sept. 11, 2012) ("There is no legal basis for rewriting the prior art to create a hindsight anticipation."). Petitioner fails to show that the disclosures in Adis are arranged as in the Challenged Claims of the '338 Patent.

## VII. GROUNDS 1-5: PETITIONER FAILS TO ESTABLISH THAT ITS REFERENCES DISCLOSE A "METHOD FOR TREATING"

While Petitioner posits that a suggestion of efficacy is sufficient for

anticipation (Paper 1, 39, 45, 50, 54), the Federal Circuit has held that "the question is not whether a prior art reference suggests the claimed subject matter …. Rather the dispositive question regarding anticipation is whether [the POSA] would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference." *AstraZeneca LP v. Apotex*, 633 F.3d 1042, 1055 (Fed. Cir. 2010). Here, the POSA would not understand Petitioner's references to disclose a "method for treating"—either expressly or inherently.[14] Ex.2048, ¶¶48-61.

### A. Petitioner's References Do Not Expressly Disclose "A Method for Treating"

Petitioner's references—review articles (Dixon and Adis), a press release (Regeneron (8-May-2008)), and clinicaltrials.gov records regarding planned trials (NCT-795 and NCT-337), merely discuss prospective studies "designed to evaluate the efficacy and safety of VEGF Trap-Eye" administered according to a specified dosing regimen. Ex.1013, 1. None of Petitioner's Ground 1-5 references discloses a "method for treating" or provides any ***data*** showing that the claimed Q8 dosing

[14] *See, e.g.*, *Novartis Pharms. Corp. v. Accord Healthcare, Inc.*, No. 18-1043-KAJ, slip op. at 37 (D. Del. Aug. 10, 2020) ("A person of skill would not have read Kappos 2006 as disclosing a treatment for RRMS [because it] describes only an early-stage clinical trial, it is too theoretical to be enabled."), *aff'd*, 21 F.4th 1362 (Fed. Cir. 2022).

regimen would effectively treat. Ex.2048, ¶¶48, 51, 56, 60; *see also* Ex.2129 (Gerritsen Tr.), 33:24-35:7; 42:8-16 (agreeing that Regeneron (8-May-2008) and Adis do not disclose efficacy data).

### B. Petitioner's References Do Not Inherently Disclose "A Method for Treating"

Because "treating" is not expressly disclosed in any of its references, Petitioner must show that "treating" is inherent in the prior art disclosure. However, it is well-established that "[a]n invitation to investigate" as disclosed in Petitioner's Ground 1-5 references "is not an inherent disclosure." *Metabolite Lab'ys Inc. v. Lab'y Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004). The Federal Circuit has made clear that "[i]nherency may not be established by probabilities or possibilities" and the "mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d at 581 (emphasis added). Instead, the disclosure must show that the limitation is the natural result of performing the claim or is necessarily present. *Id*.; *see also Continental Can*, 948 F.2d at 1268. Because the recited "method for treating" is not the necessary result of carrying out the disclosures set forth in Petitioner's Ground 1-5 references, Petitioner cannot show this limitation is inherently present.

#### 1. Knowledge of the "VEGF Trap-Eye" Amino Acid Sequence Would Not Necessarily Result in Treatment

Even if the POSA knew the amino acid sequence of "VEGF Trap-Eye" (which is disputed), due to the inherent variability in protein production, the POSA

would not necessarily produce a VEGF Trap-Eye protein that could treat an angiogenic eye disorder according to the claimed dosing regimen. Ex.2049, ¶¶90-93; Ex.2048, ¶¶92-95; Ex.2071, 90. In particular, variations in fusion protein production may result in misfolding, aggregation, truncation due to proteolytic cleavage, and/or various changes in covalent post-translational modifications. Ex.2049, ¶92; Ex.2048, ¶¶93-94; Ex.2072, 3. All of these challenges in the production and purification of intact proteins are known to affect the stability and biological activity of recombinant proteins. Ex.2049, ¶93; Ex.2048, ¶¶93-94;.

[redacted]

Another challenge to obtaining VEGF Trap-Eye protein is that "post-translational modifications of a protein can affect the biologic activity of a protein *in vivo*." Ex.2130 (Albini Tr.), 110:4-8. Specifically, VEGF Trap-Eye belongs to a class of proteins referred to as glycoproteins—*i.e.*, proteins that have been post-translationally glycosylated with, for example, sialic acid. Ex.2049, ¶95; Ex.2048, ¶97; Ex.2058, 3500. For glycoproteins like VEGF Trap-Eye, changes in host cell and culture conditions were known in the art to greatly affect the pattern and extent

of glycosylation of the expressed protein. *Id*. Moreover, the presence and quantity of sialic acid residues incorporated post-translationally into a protein were known to affect "absorption, serum half-life, and clearance from the serum, as well as the physical, chemical and immunogenic properties of the respective glycoprotein." Ex.2049, ¶96; Ex.2048, ¶¶97; Ex.2058, 3499.

[redacted]

[redacted] While the manufacture of therapeutic biologics is notoriously variable, these real-world examples demonstrate that even if the POSA had known the amino acid sequence of VEGF Trap-Eye, that knowledge alone would not necessarily result in a VEGF Trap-Eye protein that could provide treatment of an angiogenic eye disorder according to the claimed dosing regimen of the '338 Patent. Ex.2049, ¶105; Ex.2048, ¶¶103-104.

*Rapoport v. Dement*, 254 F.3d 1053 (Fed. Cir. 2001), is instructive. There, the claim-at-issue was directed to a method of treating sleep apneas by administering a particular type of compound to a patient in need of treatment, and the claim preamble—"treatment of sleep apneas"—was limiting. *Id*., 1059. The Court found that the claim was not inherently anticipated because the reference did not disclose that administration of the recited compound "would necessarily result in a 'therapeutically effective amount'" of buspirone treatment for the purpose of treating the underlying sleep apnea disorder." *Id*., 1062-63. The court continued by stating that the "mere fact that a certain limitation *may* result from a given set of circumstances is not sufficient." *Id*., 1063; *see also Galderma Lab'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 846 (2020) (variation in formulation "will

undoubtably affect the results achieved" and finding "no basis for us to conclude with certainty that all" formulations "will inevitably achieve the claimed efficacy limitations"); *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) ("Occasional results are not inherent.").

Here, as in *Rapoport*, Petitioner's references do not disclose a VEGF Trap-Eye protein that, when administered on the recited dosing schedule, necessarily results in treatment of an angiogenic eye disorder. *See* Ex.2049, ¶105 (unpredictability in the production of VEGF Trap-Eye can result in a protein that would not provide treatment of an angiogenic eye disorder according to the claimed dosing regimen of the '338 Patent); Ex.2048, ¶¶103-104. Petitioner's Ground 1-5 references do not inherently disclose a "method for treating" as recited in the Challenged Claims because they do not disclose a VEGF Trap-Eye protein that, when administered according to the claimed dosing regimen, necessarily results in treatment of an angiogenic eye disorder. Ex.2049, ¶105; Ex.2048, ¶¶103-104.

**2. Administration of "VEGF Trap-Eye" Using the Disclosed Dosing Regimen Would Not Necessarily Result in Treatment**

Even if "VEGF Trap-Eye" is made correctly, properly purified, and formulated, administration according to the disclosed regimen will not necessarily result in an effective treatment for all patients with angiogenic eye disorders.

It is well established that "[t]he mere fact that a certain limitation ***may*** result from a given set of circumstances" set forth in a prior art reference "is not sufficient"

for inherent anticipation. *Rapoport*, 254 F.3d at 1063 (citing *In re Oelrich*, 666 F.3d at 581-82). Rather, the prior art must establish that practice of prior art reference "would necessarily result" in the claimed limitation. *Id*.; *see also MEHL/Biophile,* 192 F.3d at 1365 ("Occasional results are not inherent."). As discussed below, practice of the dosing regimens disclosed in Petitioner's Grounds 1-5 references would not necessarily result in effective treatment for all patients with angiogenic eye disorders.

**a. The disclosed dosing regimen will not necessarily result in treatment for some patients**

The claimed treatment method provides a high level of efficacy (non-inferior to ranibizumab) on a Q8 maintenance dosing regimen. *See supra* Section IV.B. However, VEGF Trap-Eye dosed Q8 will not necessarily result in effective treatment (non-inferior to standard-of-care) for some sub-populations of wAMD patients. Ex.2048, ¶¶109-121.

For example, a retrospective analysis of VIEW 1/2 showed that 8-week maintenance dosing was significantly less effective than monthly dosing in approximately 20% of subjects with early persistent fluid. Ex.2048, ¶¶110-111 (citing Ex.2018, 1861); Ex.2050, ¶85. These data established that administration of VEGF Trap-Eye under the disclosed dosing regimen did not result in effective treatment—*i.e.*, patients received treatment that was inferior to Lucentis dosed monthly—in about 20% of patients. Ex.2048, ¶¶110-111.

In addition, certain sub-populations of patients—those with a history of

uveitis, prior trabeculectomy or other filtration surgery, or aphakia with absence of posterior capsule—would not necessarily receive effective treatment using the disclosed Q8 dosing regimen. Ex.2048, ¶¶112-121. Increased clearance of intravitreally administered drugs, like VEGF Trap-Eye, has been observed in people with uveitis, prior trabeculectomy or other filtration surgery, and aphakia with absence of posterior capsule. Ex.2048, ¶¶115-120; *see also* Ex.2130 (Albini Tr.), 128:6-11; 132:4-133:10. As a result, the POSA would not expect patients with these pre-existing conditions to necessarily be treated by a Q8 dosing regimen. Ex.2048, ¶¶112-121. These subpopulations were excluded from the VIEW studies, but are not excluded by the prospective dosing regimens disclosed in Petitioner's Grounds 1-5 references. *See* Ex.1001, 10:49-11:13; Ex.2048, ¶¶112-113.

**b. Even using Petitioner's extremely low bar for efficacy, the disclosed dosing regimen will not necessarily result in treatment for some patients**

Even using Petitioner's proposed incredibly low standard for treatment efficacy, some study subjects who received VEGF Trap-Eye in the 2Q8 dosing arm of VIEW 1/2 (in accordance with the dosing regimen disclosed by Petitioner's references) did not receive treatment, *i.e.*, they lost more than 15 letters as measured by ETDRS in the first 52 weeks of the study. Ex.1002, ¶43; Ex.2048, ¶¶106-108 (citing Ex.1018). [redacted] Thus, even employing

Petitioner's incorrect definition for treatment, administration of VEGF Trap-Eye under the prospective Q8 dosing regimen disclosed by Petitioner's references will not necessarily result in treatment of patients with wAMD. *See Galderma*, 799 F. App'x at 846 (Challenger "did not demonstrate that the use of any such formulation inevitably results in the claimed efficacies."); *see also Rapoport*, 254 F.3d at 1063 ("The mere fact that a certain limitation may result from a given set of circumstances is not sufficient" for inherent anticipation.).

Because "treating" is a positive limitation of the Challenged Claims and the prospective Q8 dosing regimen disclosed by Petitioner's references will not necessarily result in treatment under either's party's proposed construction, Petitioner cannot demonstrate inherency on this record. *See Rapoport*, 254 F.3d at 1063 ("The mere fact that a certain limitation *may* result from a given set of circumstances is not sufficient" for inherent anticipation.); *see also Gilead Scis., Inc. v. United States*, IPR2019-01455, Paper No. 16, at 41-42 (P.T.A.B. Feb. 5, 2020) (finding the possibility, even if "unlikely," that an individual receiving the claimed combination therapy could not be "protected from infection," "undermine[d] inherency, which 'may not be established by probabilities or possibilities.'"); *Celltrion, Inc. v. Genentech, Inc.*, IPR2016-01667, Paper No. 15, at 9-10 (P.T.A.B. Mar. 2, 2017) (inherency does not follow "even from a very high likelihood that a prior art method will result in the claimed invention") (citing *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995) (no inherent

anticipation because practice of the prior art method "could yield crystals of either polymorph")).

### C. Petitioner's References Do Not Anticipate Because They Do Not Disclose a Recognized Utility

Petitioner argues that its references anticipate the Challenged Claims because "anticipation does not require actual performance of suggestions in a disclosure" and "proof of efficacy is not required in order for a [prior art] reference to be enabled for purposes of anticipation." Paper 1, 38. However, the line of cases on which Petitioner relies—starting with *In re Hafner*, 410 F.2d 1403, 1405 (C.C.P.A. 1969), and continuing with, *e.g.*, *Rasmusson v. SmithKline Beecham Corp*., 413 F.3d 1318, 1326 (Fed. Cir. 2005)—overlooks Supreme Court jurisprudence requiring prior art to demonstrate utility in order to anticipate. In the context of § 102(b) on-sale art, the Supreme Court has required demonstration of utility to anticipate, which has been extended to public use art as well. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67-68 (1998); *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1379-80 (Fed. Cir. 2005) (extending "ready for patenting" to public use art). Furthermore, Petitioner's references fail to anticipate because they describe experimental uses which the Supreme Court has held do not constitute prior art.

The Supreme Court's requirement that on-sale bar art demonstrate utility should apply equally to other forms of § 102 prior art, including printed publications. In *Pfaff*, the Supreme Court interpreted the term "invention" in § 102 to require complete conception and to be "ready for patenting." 525 U.S. at 67-68.

Regardless of whether the "ready for patenting" art is reduced to practice or enabled, utility is required. *See id.; see also Atlanta Attachment Co. v. Leggett & Platt, Inc.*, 516 F.3d 1361, 1367 (Fed. Cir. 2008) (holding that a reduction to practice requires utility); *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999) (holding that the enablement prong of § 112 incorporates as a matter of law the utility requirement of 35 U.S.C. § 101); *Rasmusson*, 413 F.3d at 1322-23 (same).

The Patent Statute confirms that patentable inventions require utility. *See* 35 U.S.C. § 101 ("Whoever invents or discovers any new and ***useful*** process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.") (emphasis added); *see also Brenner v. Manson*, 383 U.S. 519, 528-529, 536 (1966) ("Our starting point is the proposition, neither disputed nor disputable, that one may patent only that which is 'useful.'"; "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."); *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1372-75 (Fed. Cir. 2008) (invention was not "ready for patenting" until completion of phase III clinical trials, because trials were necessary to determine whether compound would work for intended purpose).

*Pfaff's* reasoning is based on the term "invention" in 35 U.S.C. § 102 (b), which states:

> "A person shall be entitled to a patent unless —
>
> ***
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or …."

35 U.S.C. § 102 (pre-AIA). Indeed, the Federal Circuit has consistently held that a completed "invention" requires conception and reduction to practice (either actual or constructive, *i.e.*, ready for patenting). *See Solvay S.A. v. Honeywell Int'l Inc.*, 742 F.3d 998, 1000 (Fed. Cir. 2014); *In re DeBaun*, 687 F.2d 459, 463 (C.C.P.A. 1982). *Pfaff's* interpretation of "invention" in § 102 should apply to all types of art; consequently, printed publications must be "ready for patenting" in order to anticipate—*i.e.*, they must demonstrate utility to anticipate. Because Petitioner's allegedly anticipatory references do not include any results that correspond to a dosing regimen encompassed by the Challenged Claims, they have not demonstrated utility, and thus cannot anticipate.

In addition, the Supreme Court's precedent that experimental uses do not constitute prior art should apply with equal force to printed publications that merely disclose such experimental uses. The Supreme Court has explained that "[t]he use

of an invention by the inventor himself, or of any other person under his direction, by way of experiment, and in order to bring the invention to perfection, has never been regarded as [a public] use." *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 134 (1877). The experimental use exception has been extended to on-sale bar prior art as well. *Barry v. Medtronic, Inc.*, 914 F.3d 1310, 1331 (Fed. Cir. 2019) ("[E]xperimental use negates applicability of the on-sale bar, as it does the public-use bar.").

Likewise, non-secret use of an invention for experimental purpose is not anticipatory if the inventor retains control of the invention. *See, e.g.*, *City of Elizabeth*, 97 U.S. at 134 (road paving patent not anticipated where inventor publicly tested road to perfect invention's durability before priority date, explaining "[t]he use of an invention by the inventor himself, or of any other person under his direction, by way of experiment, and in order to bring the invention to perfection, has never been regarded as [a public] use."); *see also Barry*, 914 F.3d at 1329; *TP Lab'ys, Inc. v. Pro. Positioners, Inc.*, 724 F.2d 965, 971-72 (Fed. Cir. 1984).

The experimental use doctrine has been applied to the initiation of clinical trials where the inventor retains control of the invention and is merely using the invention for experimental purposes. S*ee, e.g.*, *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1380-81 (Fed. Cir. 2006) (affirming district court holding that clinical trials were "experimental[] use that negated any section 102 bar" to claims directed to compound and use thereof to treat schizophrenia). The

Federal Circuit has held that "[t]he use of an invention by the inventor himself, or of any other person under his direction, by way of experiment, and in order to bring the invention to perfection, has never been regarded as [a public] use." *Id*.; *see also Dey, L.P. v. Sunovion Pharm., Inc.*, 715 F.3d 1351, 1356-60 (Fed. Cir. 2013) (declining to grant summary judgment that Phase 3 trial was public use where participants were not informed about the formulation of the administered study drug and test administrators were subject to confidentiality protocols); *Janssen Pharmaceutical, N.V. v. Eon Labs Mfg., Inc.*, 134 F. App'x 425, 430-31 (Fed. Cir. 2005) (clinical trials were not considered public use because they were closely monitored by investigator, strict protocol was used, drug administration was restricted, and unused drug had to be returned). Accordingly, because the experimental use doctrine should apply to printed publications, and because Mylan's references only disclose the initiation and design of studies for which Regeneron retained control[15] and were being performed to perfect the invention encompassed by the Challenged Claims, they describe a use that is merely experimental, and cannot anticipate.

There is no reason to treat printed publications differently than other § 102

[15] As noted in Section V above, it is undisputed that Regeneron's prospective Phase 3 trials that are disclosed in Petitioner's references were conducted under strict confidentiality requirements.

art. Whether a use is performed (*e.g.*, a clinical trial is initiated) or disclosed in a printed publication (*e.g.*, a prospective clinical trial protocol discloses a dosing regimen), should not dictate whether the activity is anticipatory. The policy rationale behind the experimental use exception, *i.e.*, to allow an inventor to perfect her invention before applying for a patent, is furthered regardless of whether the experimentation is performed or described.

The mere initiation of Regeneron's Phase 3 trials does not anticipate the Challenged Claims because the claimed treatment method was not "ready for patenting" and the trials were for experimental purposes to perfect the invention. *See In re Omeprazole Patent Litig*., 536 F.3d at 1372-75 (invention was not "ready for patenting" until completion of Phase 3 clinical trials, because trials were necessary to determine whether compound would work for intended purpose). Accordingly, the description of the initiation of a Phase 3 trial in a press release or other publication should not anticipate merely because it was disclosed in a printed publication.

## VIII. GROUND 6: PETITIONER FAILS TO DEMONSTRATE THAT ANY CHALLENGED CLAIM IS OBVIOUS BASED ON DIXON

Petitioner fails to show that there is a reasonable likelihood that at least one of the Challenged Claims is unpatentable as obvious based on Dixon, either alone

or in combination with the '758 Patent or Dix.[16] Petitioner argues that Dixon's disclosure of Regeneron's Phase 2 CLEAR-IT 2 clinical trials results and the initiation of a Phase 3 trial would have provided the POSA with a reasonable expectation of success in the claimed dosing regimen. Paper 1, 64-65. Neither argument has merit.

The CLEAR-IT 2 trial results would ***not*** have provided the POSA with a reasonable expectation of success; to the contrary, these data suggested that VEGF Trap-Eye would ***not*** be effective on a Q8 dosing regimen. Ex.2050, ¶¶120-127. Likewise, Regeneron's initiation of a Phase 3 trial also does not evidence a reasonable expectation of success, particularly since the study design itself shows Regeneron's uncertainty regarding the success of a Q8 dosing regimen. Ex.2050, ¶¶114-119. Given the history of failures with extending dosing of anti-VEGF

[16] As discussed *supra* in Section V.B.2.c., the '758 Patent and Dix disclose VEGF $Trap_{R1R2}$ sequences that do not satisfy the sequence limitations of the Challenged Claims. Petitioner fails to supply any argument or evidence to explain why the POSA would have been motivated to select the claimed VEGF Trap sequences over other disclosed but unclaimed VEGF Trap sequences. *See Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (holding that "hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention" is not permissible).

agents in the art, even Dixon recognizes that the durability of VEGF Trap-Eye and its adoption in clinical practice would only be known after Regeneron's Phase 3 clinical trial results are reported. Ex.2050, ¶¶128-130; Ex.1006, 1577.

In fact, Mylan's expert, Dr. Albini, admitted in deposition that the POSA would have considered PRN to be a better dosing strategy than the proposed Q8 regimen of VIEW given the failures with extended dosing in the art:

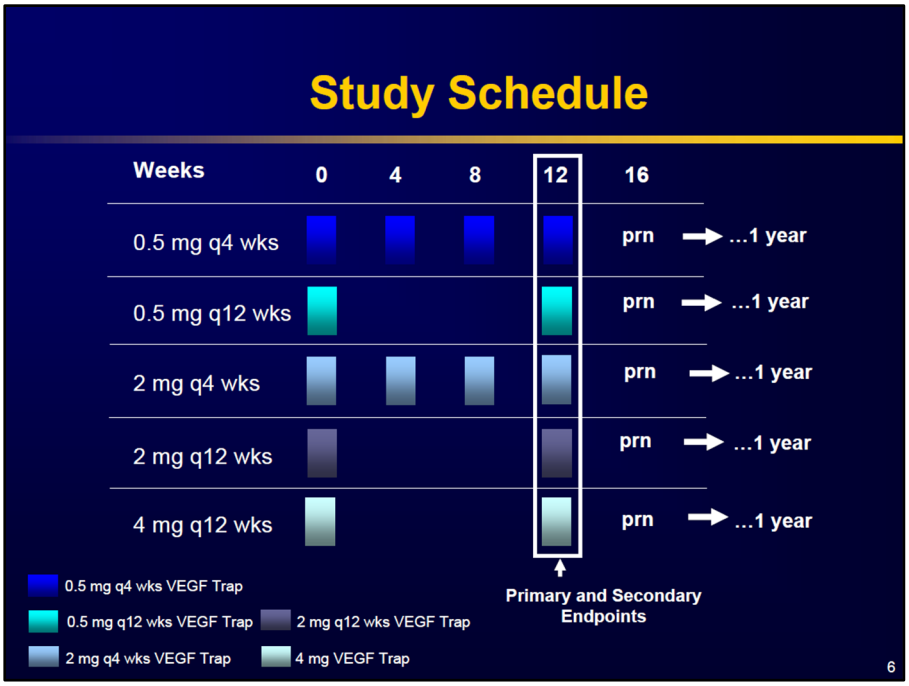
> Q. …Why wouldn't [the POSA] just use three monthly loading doses followed by Q8 dosing if they saw the protocol for the VIEW study?
> A. I think that because of the relative lack of efficacy seen with quarterly dosing and less frequent regular dosing, that PRN dosing at the time was considered to be a better strategy.
> Q. Were people doing Q8 maintenance dosing at the time?
> A. I've already answered that many times, but the answer is no.

Ex.2130 (Albini Tr.), 283:13-284:7 (objections omitted).

Finally, the long-felt need and failure in the art to develop an extended dosing regimen, coupled with the rapid adoption and tremendous commercial success that EYLEA has enjoyed since launch all confirm the non-obviousness of the claimed dosing regimen. Ex.2050, ¶¶110-113, 150-181, Ex.2052 ¶¶48-85.

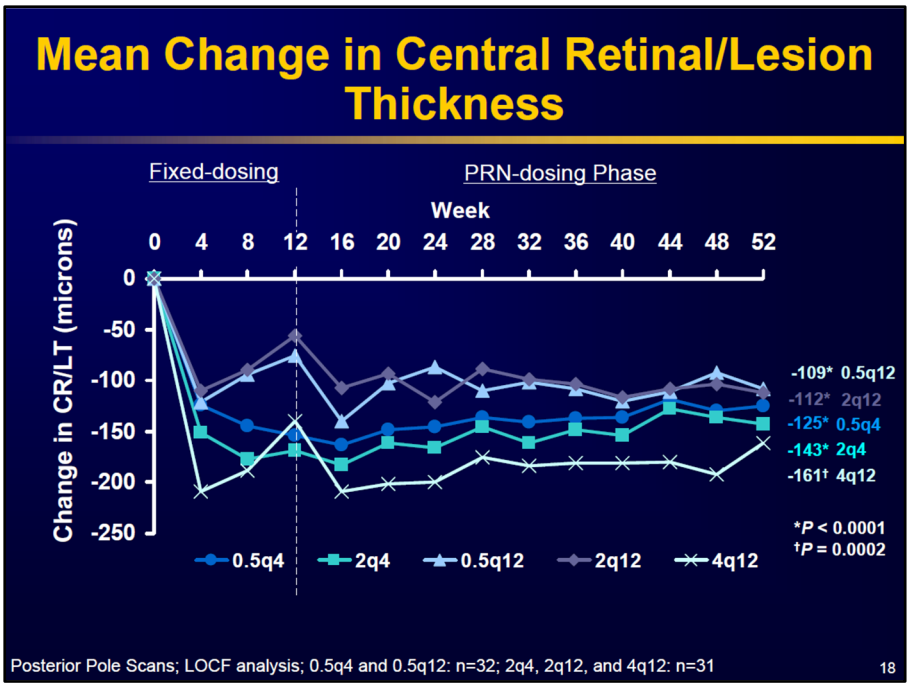
### A. The POSA Would Not Have Had a Reasonable Expectation of Success

***First***, CLEAR-IT 2 would not have provided the POSA with a reasonable expectation that the claimed Q8 dosing regimen would have been successful before it was tested. Ex.2050, ¶¶120–127, 73-75. CLEAR-IT 2 tested four monthly loading doses followed by PRN, as well quarterly dosing followed by PRN, as shown below:




Ex.1055, Slide 6. CLEAR-IT 2 did ***not*** test the Q8 dosing regimen that was tested in VIEW or that is claimed in the '338 Patent. Ex.2050, ¶120; Ex.2130 (Albini Tr.), 206:2-19.

The CLEAR-IT 2 data showed an increase in central retinal thickness (CRT) beginning at week 4 and continuing through week 12 in the quarterly dosing arms (0.5Q12, 2Q12, 4Q12):




Ex.1055, Slide 18; Ex.2050, ¶122; Ex.2130 (Albini Tr.), 214:17-22. An increase in CRT corresponds with fluid re-accumulation on the retina, and is a tell-tale sign that retreatment with an anti-VEGF agent is necessary. Ex.2130 (Albini Tr.), 211:1-5; Ex.2050, ¶¶122-123. The POSA would have understood that an increase in CRT between weeks 4 and 8 would strongly suggest that VEGF Trap-Eye had less than 8-week durability. Ex.2050, ¶¶122-123; Ex.2130 (Albini Tr.), 211:1-5 (fluid reaccumulation requires retreatment). Indeed, the only treatment arms that were successful in maintaining a dry retina were the monthly dosing arms (*i.e.*, 0.5Q4 and 2Q4). Ex.2050, ¶¶124-125. Rather than providing an expectation of success

for a Q8 dosing regimen, the clinical trial results from CLEAR-IT 2 would have provided a basis to doubt that VEGF Trap-Eye would be successful on an 8-week dosing schedule. Ex.2050, ¶¶124-127.

***Second***, that Regeneron chose to run Phase 3 trials does not mean that the POSA would have expected the 8-week dosing regimen to be successful.[17] Paper 1, 64. Phase 3 clinical trials, including of VEGF inhibitors for angiogenic eye disorders have regularly failed, even when Phase 2 results show promise. Ex.2050, ¶¶114-116 (citing Ex.2099, Ex.2020, Ex.2021 (lampalizumab); Ex.2022, Ex.2023, (Conbercept); Ex.2024, Ex.2025 (Fovista)).

Indeed, Regeneron's design of its Phase 3 trials demonstrates that it was hedging its bets on an extended 8-week dosing regimen. The claimed Q8 dosing regimen was one of three different dosing regimens tested in VIEW. *See* Ex.1006, 1576; Ex.2130 (Albini Tr.), 271:1-14; Ex.2050, ¶¶79, 117-119. Given the additional time and expense required to test additional treatment arms, and Regeneron's size and financial condition at the time, if Regeneron had been reasonably certain that 8-week maintenance dosing would work, it had every incentive to eliminate the 4-week VEGF Trap-Eye dosing arms. Ex.2050, ¶¶79, 117-119. In addition, Regeneron hierarchically ranked its Q8 dosing arm third out of its three dosing arms, meaning that Regeneron was least confident in the Q8

[17] *See OSI Pharms. LLC v. Apotex Inc.*, 939 F.3d 1375, 1378-79 (Fed. Cir. 2019).

dosing arm, even as compared to the 0.5Q4 arm, showing non-inferiority to monthly ranibizumab. Ex.2050, ¶¶117-119; Ex.2098, 16. Far from showing a reasonable expectation of success, the design of the Phase 3 study shows that even the sponsor did not know whether the Q8 dosing arm would meet its primary endpoint of non-inferiority to ranibizumab. Ex.2050, ¶¶117-119

***Third***, there was great uncertainty in the art regarding an extended dosing regimen based on failures in the art, as Mylan's expert, Dr. Albini acknowledges. Ex.2130 (Albini Tr.), 283:13-284:7; Ex.2050, ¶¶109-113, 153-67; Ex.1018, 2537. As discussed in Section II above, significant efforts had been undertaken in the art to extend dosing, but fixed extended dosing or PRN dosing without monthly monitoring were not effective at maintaining vision. Notwithstanding the burden of monthly office visits to patients, caregivers, and physicians, Dr. Albini concedes that given the repeated failures with extended dosing in the art, before Regeneron's Phase 3 trials, the POSA would have regarded PRN with monthly monitoring to be a better dosing strategy than the claimed Q8 dosing regimen. (Ex.2130 (Albini Tr.), 285:15-286:3, 283:13-284:7).

### B. Objective Evidence Confirms the Non-Obviousness of the Claimed Dosing Regimen

The Federal Circuit has repeatedly held that objective evidence must be considered before making an obviousness determination." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1080 (Fed. Cir. 2012). "[O]bjective considerations … guard as a check against hindsight bias,

and include evidence of long-felt but unsolved need, failure of others, unexpected results, and commercial success." *Id.*, 1078-79.

A nexus exists between the Challenged Claims and both EYLEA®'s approved dosing regimen (the "Eylea Label" or "EL") and physicians' administration of EYLEA in practice ("Physicians' Practice" or PP, and together with EL, "EL&PP"), as set forth below and as explained by Dr. Do:

| **Claim / Limitation** | **Evidence of Nexus** |
|---|---|
| Claim 1.pre./Claim 14.pre.<br>(method for treating an angiogenic eye disorder) | EL&PP are methods of treating an angiogenic eye disorder in a patient. Ex.2051, ¶¶98, 116, 135, 153. |
| Claim 1.a/Claim 14.a<br>(sequentially administering … a single initial dose … followed by one or more secondary doses … followed by one or more tertiary doses …) | EL&PP involve sequential administration of an initial dose, followed by one or more secondary doses, followed by one or more tertiary doses of EYLEA, which is a VEGF antagonist. Ex.2051, ¶¶99, 117, 136, 154. |
| Claim 1.b/Claim 14.b<br>(each secondary dose is administered 2 to 4 weeks after the immediately preceding dose)<br>Claim 3.b/Claim 16.b (each secondary dose is administered 4 weeks after the immediately preceding dose) | In the EL&PP, each secondary dose is administered every 4 weeks (approximately 28 days, monthly) after the immediately preceding dose. Ex.2051, ¶¶100, 104, 118, 122, 137, 141, 155, 159. |
| Claim 1.c/Claim 4/Claim 14.c/Claim 17<br>(each tertiary dose is administered [at least] 8 weeks after the immediately preceding dose)<br><br>Claim 5/Claim 19<br>(at least 5 tertiary doses…are administered...the first four tertiary doses are administered 8 weeks after the | In the EL&PP, each tertiary dose is administered every 8 weeks (2 months) after the immediately preceding dose. Ex.2051, ¶¶101, 105, 119, 123, 138, 142, 156, 160.<br><br>EL&PP involve administration of at least 5 tertiary doses of EYLEA®. Ex.2051, ¶¶106-108, 125-127, 143- |

| Claim / Limitation | Evidence of Nexus |
|---|---|
| immediately preceding dose, and … each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose) | 145, 162-164. |
| Claim 1.d (amino acid sequence)/Claim 14.d (nucleotide sequence) | Eylea has the amino acid sequence (claim 1) and nucleotide sequence (claim 14) recited. Ex.2051, ¶¶102, 120, 139, 157; Ex.1024, 6; Ex.1010, 40-42, 61, 71. |
| Claim 3.a/Claim 16.a (only two secondary doses) | EL&PP for wAMD involve administration of only two secondary doses. Ex.2051, ¶¶103, 121, 140, 158. |
| Claims 6, 7, 18, 20 (angiogenic eye disorder selected from [group consisting of / is] age related macular regeneration) | EL&PP involve administration of EYLEA to treat wAMD, DME, DR and RVO (PP only). Ex.2051, ¶¶109, 110, 124, 128, 146, 147, 161, 165. |
| Claims 8-10, 21-23 (topical or intraocular administration / intravitreal administration) | EL&PP involve intravitreal administration of EYLEA. Ex.2051, ¶¶111-113, 129-131, 148-150, 166-168. |
| Claims 11, 13, 24, 26 (dosage of 0.5/2 mg) | EL&PP involve administration of 2 mg of EYLEA. Ex.2051, ¶¶114, 115, 132, 133151, 152, 169, 170. |

Petitioner tries to erase the overwhelming evidence of long-felt but unmet need by arguing that Regeneron's testing of its own inventive dosing regimen anticipated itself: "By 2009, the claimed dosing regimen was already publicly disclosed by Regeneron itself, and thus any 'unmet' need had already been fulfilled well before the '338 patent was filed." Paper 1, 69. Petitioner disregards that it was not until ***after*** Regeneron's VIEW1/2 study results were obtained that anyone, including Regeneron, understood that the remarkable advantage of fixed 8-week

dosing could be realized. In fact, as discussed above, the art was littered with failed efforts to extend dosing of anti-VEGF agents, which made Regeneron's clinical trial results all the more unexpected. *See* Sections II and VII.A. *supra*; Ex.2050, ¶¶150-181.

Notably, Regeneron was not the first or only FDA-approved anti-VEGF therapy used by clinicians for the treatment of angiogenic eye disorders. Indeed, when EYLEA launched in late 2011, both Lucentis and off-label Avastin were standard-of-care for the treatment of angiogenic eye disorders. Nonetheless, by any measure, EYLEA has enjoyed tremendous commercial success since launch. Ex.2052, ¶¶48-85. Regeneron's U.S. sales of EYLEA, as well as EYLEA's share of sales relative to other anti-VEGF treatments, have grown significantly since launch. Ex.2052, ¶¶56-76; Ex.2039, 1; Ex.2040, 4. Moreover, the '338 Patent's claimed dosing regimen has been an important factor driving demand for EYLEA.[18]

[18] Dr. Albini asserts (without support) that EYLEA's commercial success is attributable to marketing and promotional activities or regulatory exclusivity (Ex.1002, ¶413), However, Dr. Manning's analysis concludes that EYELA's commercial success does not appear to be due to marketing efforts separate and apart from the patented dosing regimen. Ex.2052, ¶¶105-132. Moreover, regulatory exclusivity has not prevented companies from attempting (yet failing) to develop

Ex.2052, ¶¶86-104. Thus, Petitioner's assertion that the '338 Patent's claimed dosing regimens were obvious before January 2011 is contradicted by the long-felt but unmet need in the art for an extended dosing regimen, the failures in the art to develop such a regimen, the unexpected results revealed by Regeneron's Phase III clinical data that showed for the first time that Q8 dosing could maintain vision, and the extraordinary commercial success that EYLEA has enjoyed since launch. Ex.2050, ¶¶150-181; Ex.2052 ¶¶48-85.

## IX. CONCLUSION

For the foregoing reasons, Patent Owner respectfully requests that the Board affirm the validity of the Challenged Claims of the '338 Patent.

Dated: February 11, 2022

Respectfully Submitted,

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extended dosing regimens for other anti-VEGF agents. Ex.2050, ¶¶160-173 (failure of others).

## CERTIFICATE OF COMPLIANCE

The undersigned certifies that this Patent Owner Response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This Patent Owner Response (including figure labels and annotations) contains 13,935 words as calculated by the "Word Count" feature of Microsoft Word 2010, the word processing program used to create it.

The undersigned further certifies that this Patent Owner Response complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This Patent Owner Response has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14-point font.

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## CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq*., the undersigned Certifies that on February 11, 2022, a true and entire copy of this **PATENT OWNER RESPONSE**, and all supporting exhibits, were served via e-mail to the Petitioners at the following email addresses:

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