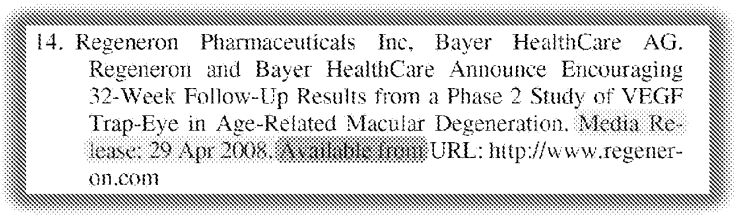
AMD. (*Id.*, 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '069 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":


14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration. Media Release: 29 Apr 2008. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron (28-September-2008) were well-known—and widely available—to the community interested in the subject matter of the '069 patent. (*See, e.g.*, *id.*, 262-63, 268-69).

59. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (28-September-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[7] Thus, a person of ordinary skill in the art could have easily accessed Regeneron (28-September-2008) via Regeneron's website and easily downloaded an electronic copy.

[7] *See, e.g.*, Ex.1056, Regeneron (28-September-2008), 1.

60. For at least these reasons, it is my opinion that Regeneron (28-September-2008) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '069 patent, exercising reasonable diligence, before 2011.

**3. April 2009 Press Release.**

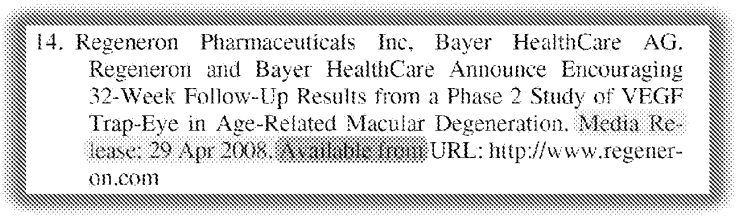
61. Regeneron issued a press release dated April 30, 2009 (Ex.1028, Regeneron (30-April-2009)), which described the extension of Regeneron's global development program for VEGF Trap-Eye to include Central Retinal Vein Occlusion ("CRVO"). (*Id.*, 1).

62. Specifically, Regeneron (30-April-2009) stated that in the Phase 3 CRVO program, GALILEO, patients would "receive 6 monthly intravitreal injections of [] VEGF Trap-Eye at a dose of 2 milligrams (mg)." (*Id.*, 1).

63. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (30-April-2009) included the experimental group that received 6 monthly intravitreal injections of VEGF Trap-Eye at a dose of 2 milligrams. (*Id.*, 1).

64. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (30-April-2009) because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with

CRVO. (*Id.*, 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '069 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":


14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration. Media Release: 29 Apr 2008. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron (30-April-2009) were well-known—and widely available—to the community interested in the subject matter of the '069 patent. (*See, e.g.*, *id.*, 262-63, 268-69).

65. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (30-April-2009) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[8] Thus, a person of ordinary skill in the art could have easily accessed Regeneron (30-April-2009) via Regeneron's website and easily downloaded an electronic copy.

[8] Ex.1028, Regeneron (30-April-2009), 1.

66. For at least these reasons, it is my opinion that Regeneron (30-April-2009) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '069 patent, exercising reasonable diligence, before 2011.

**4. February 2010 Press Release.**

67. Regeneron issued a press release dated February 18, 2010 (Ex.1057, Regeneron (18-February-2010)), which described the "DA VINCI" trial. (*Id.*, 1; *see also* Ex.1066, Bayer (18-February-2010), 1).

68. The patients in the study were randomized into five groups: four experimental groups and one control group. (Ex.1057, Regeneron (18-February-2010), 1). One of the experimental groups received "three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by . . . every 8-week dosing" while another experimental group received "three initial monthly doses of 2.0 mg of VEGF Trap-Eye (at baseline and weeks 4 and 8), followed through week 24 by . . . as needed (PRN) dosing with specific repeat dosing criteria." (*Id.*).

69. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (18-February-2010) included the two experimental groups that received 2 mg intravitreal VEGF Trap-Eye either (1) every

other month following three initial monthly injections, or (2) as needed (PRN) following three initial monthly injections. (*Id.*, 1).

70. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (18-February-2010) because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with DME. (*Id.*, 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '069 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":

> 14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration. Media Release: 29 Apr 2008. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron (18-February-2010) were well-known—and widely available—to the community interested in the subject matter of the '069 patent. (*See, e.g.*, *id.*, 262-63, 268-69).

71. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (18-February-2010) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible,

and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[9] Thus, a person of ordinary skill in the art could have easily accessed Regeneron (18-February-2010) via Regeneron's website and easily downloaded an electronic copy.

72. For at least these reasons, it is my opinion that Regeneron (18-February-2010) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '069 patent, exercising reasonable diligence, before 2011.

**5. Additional Regeneron Press Releases.**

73. Regeneron and Bayer HealthCare AG issued a press release dated March 27, 2007 (Ex.1053, Regeneron (27-March-2007)), which described the twelve-week data for a "Phase 2 randomized study of their VEGF Trap-Eye in patients with the neovascular form of age-related macular degeneration (wet AMD)." (*Id.*, 1).

74. The patients in the study were "randomized to 5 groups" where "[t]wo groups received either 0.5 or 2.0 mg of VEGF Trap-Eye administered every four weeks, and three groups received a single dose of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye." (*Id.*, 1). Furthermore, the President of Regeneron Research Laboratories was

[9] Ex.1057, Regeneron (18-February-2010), 1.

quoted as stating "[o]ur Phase 3 program is being designed to test this possibility and further evaluate the safety and efficacy of various doses and dosing intervals of the VEGF Trap-Eye." (*Id.*).

75. Regeneron and Bayer HealthCare AG issued a press release dated August 2, 2007 (Ex.1054, Regeneron (2-August-2007)) which described "a Phase 3 study of the VEGF Trap-Eye in the neovascular form of age-related macular degeneration (wet AMD)." (*Id.*, 1). Specifically, Regeneron (2-August-2007) described "VEGF Trap-Eye . . . doses . . . 2.0 mg at an eight-week dosing interval." (*Id.*).

76. Regeneron and Bayer HealthCare AG issued a press release dated April 28, 2008 (Ex.1012, Regeneron (28-April-2008)) which described the thirty-two-week results from a "double-masked, prospective, randomized, multi-center Phase 2 trial" in patients with the "neovascular form of Age-related Macular Degeneration (wet AMD)" treated with VEGF Trap-Eye. (*Id.*, 1; *see also* Ex.1067, Bayer (28-April-2008), 1).[10]

[10] I note that the information disclosed within the Regeneron Press Releases discussed herein is essentially the same as the information disclosed within the corresponding Bayer Press Releases.

77. The patients in the study were "randomized to five dose groups" as follows:

(1) monthly dose of 0.5 milligrams (mg) of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN[11] dosing schedule;

(2) monthly dose of 2.0 mg of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

(3) quarterly dose of 0.5 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule;

(4) quarterly dose of 2.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule; or

(5) quarterly dose of 4.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule.

(Ex.1012, Regeneron (28-April-2008), 1).

78. Regeneron (28-April-2008) added that VEGF Trap-Eye was being evaluated "using a monthly loading dose of . . . 2.0 mg for 12 weeks, followed by a nine-month fixed-dosing regimen of . . . 2.0 mg every eight weeks" or "monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye for 12 weeks" followed by

[11] "PRN" (or *pro re nata*) is commonly understood as "as needed" dosing.

"therapy at the same dose on a PRN dosing schedule based upon the physician assessment of the need for re-treatment." (Ex.1012, Regeneron (28-April-2008), 1-2).

79. Regeneron issued a press release dated September 14, 2009 (Ex.1068, Regeneron (14-September-2009)) which described two "Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD)," and a phase 2 trial "for the treatment of Diabetic Macular Edema (DME)." (*Id.*, 1). Specifically, Regeneron (14-September-2009) described "VEGF Trap-Eye . . . dosed . . . 2.0 mg every eight weeks (following three monthly doses)" in the phase 3 trials and dosing of "2 mg on an as-needed (PRN) basis after three monthly loading doses," in the phase 2 trial. (*Id.*).

80. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (14-September-2009) included the experimental groups that were to receive VEGF Trap-Eye "2.0 mg every eight weeks (following three monthly doses)," or "2 mg on an as-needed (PRN) basis after three monthly loading doses." (*Id.*, 1).

81. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in the above Press Releases because they pertain to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet

AMD. (*See* ¶¶ 42-43, 50, 58, 64, 70, above). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '069 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":

> 14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration. Media Release: 29 Apr 2008. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron's Press Releases were well-known—and widely available—to the community interested in the subject matter of the '069 patent. (*See, e.g., id.*, 262-63, 268-69).

82. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate these Regeneron Press Releases exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where these documents were easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[12] Thus, a person of

[12] Ex.1053, Regeneron (27-March-2007), 1; Ex.1054, Regeneron (2-August-2007), 1; Ex.1012, Regeneron (28-April-2008), 1; Ex.1068, Regeneron (14-September-2009), 1.

ordinary skill in the art could have easily accessed these Press Releases via Regeneron's website and easily downloaded an electronic copy.

83. For at least these reasons, it is my opinion that Regeneron's Press Releases outlined above were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '069 patent, exercising reasonable diligence, before 2011.

### C. CLINICALTRIALS.GOV.

84. ClinicalTrials.gov is an electronic registry and results database of clinical studies supported by the U.S. National Institutes of Health that is open and accessible to the public as a "resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions."[13] Each study record includes a summary of the study protocol. ClinicalTrials.gov includes records for several clinical studies involving aflibercept, including:

- VIEW1 (ClinicalTrials.gov identifier NCT00509795) (Ex.1014, NCT-795);

[13] Ex.1069, Background-ClinicalTrials.gov, 1-3.

- VIEW2 (ClinicalTrials.gov identifier NCT00637377) (Ex.1015, NCT-377); and
- GALILEO (ClinicalTrials.gov identifier NCT01012973) (Ex.1029, NCT-973).

85. NCT-973 (GALILEO) was first available as of at least July 22, 2010 and describes a clinical study titled "A Randomized, Double-masked, Sham-controlled Phase 3 Study of the Efficacy, Safety and Tolerability of Repeated Intravitreal Administration of VEGF Trap-Eye in Subjects With Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)." (Ex.1029, NCT-973, 5; Ex.1070, Wayback-Affidavit-069 (Wayback Machine records showing public availability of NCT-973 prior to Jan. 13, 2011); Ex.1071, Holz, 278 ("GALILEO is a phase III, randomised, double-masked, multi-centre clinical study . . . registered as NCT01012973 on clinicaltrials.gov").[14] NCT-973 lists the following experimental "arms" of the study:

[14] *See also* Ex.1014, NCT-795, 3; Ex.1070, Wayback Affidavit-069 (Wayback Machine records showing public availability of NCT-795, describing a clinical study titled "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration," prior to Jan. 13,

| | |
|---|---|
| Experimental: Arm 1<br><br>VEGF Trap-Eye Intravitreal Injection | Intravitreal injection. Weeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up. |
| Sham Comparator: Arm 2<br><br>Sham treatment | Sham treatment. Weeks 0 to 20 sham treatment every 4weeks; weeks 24 to |

2011); Ex.1018, Heier-2012, 2539 ("Patients in VIEW 1 (registered at www.clinicaltrials.gov on July 31, 2007 . . . "); Ex.1015, NCT-377, 3-4; Ex.1070, Wayback-Affidavit (Wayback Machine records showing public availability of NCT-377, describing a clinical study titled "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)," prior to Jan. 13, 2011); Ex.1018, Heier-2012, 2539 ("Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008 . . . ")).

| | |
|---|---|
| | 48 every 4 weeks re-assessment and sham injection; weeks 52 to 100 safety follow-up. |

(Ex.1029, NCT-973, 5).[15] The experimental arms above included the group which required participants to receive "[w]eeks 0 to 20 injection of VEGF Trap-Eye every 4 weeks; weeks 24 to 48 every 4 weeks re-assessment and either (PRN) injection of VEGF Trap-Eye or sham injection; weeks 52 to 100 safety follow-up." (*Id.*).[16]

86. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in NCT-973 included the experimental group that

[15] *See also* Ex.1014, NCT-795, 6-8 (Experimental Arms 1-3); Ex.1015, NCT-377, 6 (Experimental Arms 1-3).

[16] *See also* Ex.1014, NCT-795, 8 (experimental arms included the group which required participants to receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year"); Ex.1015, NCT-377, 6 (experimental arms included the group which required participants to receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year").

received VEGF Trap-Eye every four weeks for twenty weeks followed by "(PRN) injection of VEGF Trap-Eye." (Ex.1029, NCT-973, 5).[17]

87. A person of ordinary skill in the art would have been interested in and easily accessed and sought out the information disclosed on the ClinicalTrials,gov website regarding NCT-795, NCT-377, and NCT-973 because they each pertain to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (Ex.1014, NCT-795, 3; Ex.1015, NCT-377, 3-4; Ex.1029, NCT-973, 3). Thus, in my opinion, NCT-795, NCT-377, and NCT-973 were all "publicly accessible" as they were disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art of the '069 patent, exercising reasonable diligence, could locate them.

88. My opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '069 patent that expressly cited to clinical trial

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[17] *See also* Ex.1014, NCT-795, 8 (including the experimental group that received VEGF Trap-Eye 2.0 mg every two months "including one additional 2.0 mg dose at Week 4"); Ex.1015, NCT-377, 6 (included the experimental group that received VEGF Trap-Eye 2.0 mg every two months "including one additional 2,0 mg dose at Week 4").

records from ClinicalTrials.gov, including NCT-795, NCT-377, and NCT-973. For example, Reichert (Ex.1072, Reichert)[18] provides the following disclosures of NCT-795, NCT-377, and NCT-973:

> (Lucentis®, Genentech). In the 4 arm VIEW 1 study [NCT00509795], adult patients (50 years and older) in arms 1 and 2 are administered either 0.5 or 2.0 mg aflibercept every four weeks for 1 year, then the same dose is administered as frequently as every four weeks but no less frequently than every 12 weeks. Patients

(*Id.*, 94 (emphasis added));

> is September 2013. The on-going VIEW 2 [NCT00637377] has the same design as VIEW 1, but is being conducted at sites in Europe, Asia Pacific, Japan and Latin America by Bayer. A total of 1,211 patients were recruited; the estimated study completion date is August 2011.

(*Id.*, 95 (emphasis added); *see also id.*, 96); and

[18] Ex.1072, Reichert, 76; *see also id.*, cover (Reichert is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '069 patent).

> In the placebo-controlled GALILEO study [NCT01012973], patients in the experimental arm receive intravitreal injections of aflibercept every four weeks during weeks 0–20, every four weeks during weeks 24 to 52 plus additional injections of either aflibercept or placebo on week 60 and 68 at re-assessment.

(*Id.*, 95 (emphasis added)). Moreover, Reichert makes multiple, express references to obtaining information online directly from ClinicalTrials.gov. (*Id.*, 79 (Table 7 ("listed on clinicaltrials.gov")); *id.*, 99 (Ref. No. 69 (citing ClinicalTrials.gov record and corresponding internet address))).

89. Similarly, Anderson (Ex.1073, Anderson)[19] provides the following disclosures of NCT-795 and NCT-377 online reports:

> Two phase III clinical trials are underway (VIEW-1 in the USA and Canada and VIEW-2 in Europe, Asia-Pacific, Japan and Latin America). These non-inferiority studies aim to compare efficacy of VEGF Trap against ranibizimab. Study completion is expected in 2012 and 2011, respectively (http://clinicaltrials.gov/ct2/show/NCT00509795; http://clinicaltrials.gov/ct2/show/NCT00637377). The effect of VEGF Trap on DMO is in phase II clinical testing (http://clinicaltrials.gov/ct2/show/NCT00789477). Table 1 also

[19] Ex.1073, Anderson, 272 (Anderson is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '069 patent).

(*Id.*, 275 (emphasis added)). Anderson made additional references to obtaining information from ClinicalTrials.gov. (*Id.*, 272-77, 280; *see also id.*, 373 (Figure 1 ("Graph displaying the number of clinical trials registered with the ClinicalTrials.gov registry (http://clinicaltrials.gov) each year between 2001 and 2009."))).

90. Another example, Ciulla (Ex.1074, Ciulla),[20] provides the following:

> 52 ($P < 0.0001$ for both from baseline). Currently, two randomized, international phase III studies (VIEW-1 and VIEW-2) (http://www.clinicaltrials.gov; NCT00509795, NCT00637377) are comparing intravitreal VEGF trap with ranibizumab.

(*Id.*, 162 (emphasis added)). Ciulla also made numerous other references to ClinicalTrials.gov and obtaining information from that database. (*Id.*, 162-63).

91. Ni (Ex.1075, Ni)[21] provided the following:

[20] Ex.1074, Ciulla, 158 (Ciulla is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '069 patent).

[21] Ex.1075, Ni, 401 (Ni is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '069 patent).

27 Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects with Wet AMD (VIEW 1). http://www.clinicaltrials.gov/ct2/show/NCT00509795?order=1 (accessed July 31, 2007).

28 Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2). http://clinicaltrials.gov/ct2/show/NCT00637377?order=1 (accessed March 12, 2008).

(*Id.*, 409 (emphasis added)). Additionally, Ni references numerous clinical trials with citations to ClinicalTrials.gov as the source of the information. (*See, e.g.*, *id.*, 408-10).

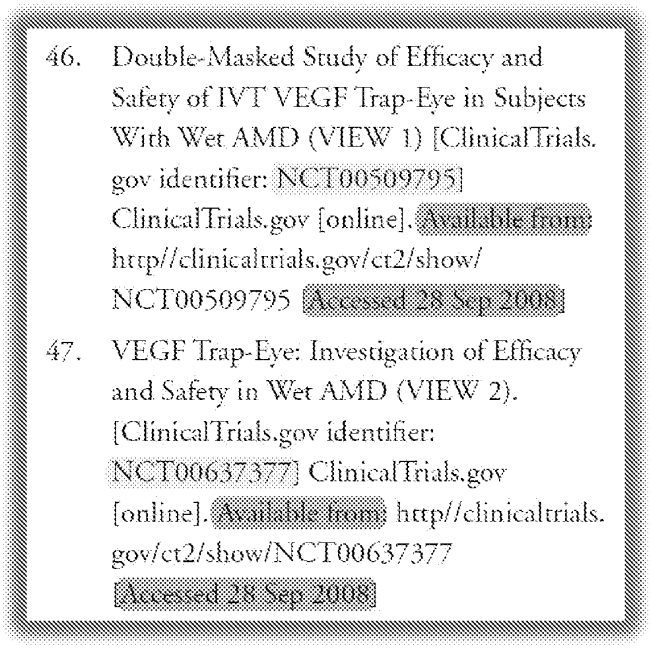
92. Another example, Zarbin (Ex.1076, Zarbin)[22] provided the following:

in a Phase 1 clinical trial.[150] VEGF Trap-Eye (http://clinicaltrials.gov/ct2/show/NCT00509795?term=VEGF+Trap-Eye&rank=14) is formulated for intravitreal injection, appears to be effective in a Phase 2 trial (www.bmctoday.net/retinatoday/2009/10/article.asp?f=1009_08.php), and is now being compared with ranibizumab in a Phase 3 clinical trial. AAV2-sFLT01

[22] Ex.1076, Zarbin, 1350 (Zarbin is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '069 patent).

(*Id.*, 1360 (emphasis added)). Additionally, Zarbin also references numerous clinical trials with citations to ClinicalTrials.gov as the source of the information. (*See id.*, 1351-52, 1356-62).

93. Dixon (Ex.1006, Dixon)[23] provides the following citations, further confirming that both NCT-795 and NCT-377, including the dosing regimens disclosed therein, were publicly available as of at least September 28, 2008:



46. Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) [ClinicalTrials.gov identifier: NCT00509795] ClinicalTrials.gov [online]. Available from: http//clinicaltrials.gov/ct2/show/NCT00509795 [Accessed 28 Sep 2008]

47. VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2). [ClinicalTrials.gov identifier: NCT00637377] ClinicalTrials.gov [online]. Available from: http//clinicaltrials.gov/ct2/show/NCT00637377 [Accessed 28 Sep 2008]

(*Id.*, 1579 (emphasis added)). Accordingly, it is my firm opinion that ClinicalTrials.gov records, NCT-795, NCT-377, and NCT-973, were well-known—

[23] Ex.1006, Dixon, 1573 (Dixon is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '069 patent).

and widely available—to the community interested in the subject matter of the '069 patent.

94. Prior to 2011, a person of ordinary skill in the art would have also been able to locate NCT-795, NCT-377, and NCT-973 exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to the ClinicalTrials.gov website where the documents were easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[24] Thus, a person of ordinary skill in the art could have easily accessed NCT-795, NCT-377, and NCT-973 via ClinicalTrials.gov and easily downloaded an electronic copy of each.

95. For the reasons outlined above, a person of ordinary skill in the art would have considered the posting dates cited at ClinicalTrials.gov to be trustworthy and authoritative and it is my opinion that NCT-795, NCT-377, and NCT-973 were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '069 patent, exercising reasonable diligence, before 2011.

[24] *See* Ex.1014, NCT-795, 1; Ex.1015, NCT-377, 1; Ex.1029, NCT-973, 1.

D. SEC FILINGS.

96. As I note above (*see* ¶¶ 41-44), company press releases were well-known, and widely available, to persons of ordinary skill in the art. This was especially true of persons of ordinary skill in the art of the '069 patent, who expressly cited Bayer and Regeneron press releases. (*See, e.g.*, Ex.1007, Adis, 262-63, 268-69).

97. Moreover, domestic publicly-traded companies are required to file certain forms with the SEC, and this is well-known by those in the pharmaceutical industry and academia. A company's SEC filings provide "reliable information about [the company]" that allows a person in the art to ensure that they are well informed and up-to-date on all of the most important developments. (Ex.1077, Corporate Finance Institute, 1-3; *see also* Ex.1078, Schneider, 258 (noting that "SEC filings . . . have been considered to be among the most accurate and reliable . . . sources of information available"); Ex.1079, Kuepper, 1-4).

98. SEC filings, such as a company's Form 10-Q, are easily accessible via the Electronic Data Gathering, Analysis, and Retrieval system ("EDGAR") or a company's website. (*See, e.g.*, Ex.1080, Zucchi). SEC filings provide, *inter alia*, information regarding the company's finances as well as recent business activity. (*See id.*; Ex.1081, Hayes, 3-4, 8-10).

99. In my experience in the industry, SEC filings for pharmaceutical or biotechnology companies included information regarding ongoing development of different products, including ongoing clinical trials and the results of completed clinical trials. Thus, a person of ordinary skill in the art would utilize the information contained therein, amongst other references, to keep up to date on the development in the field of interest, especially with direct competitors.

100. First, a person of ordinary skill in the art would be interested in such "Financial and Operating Results" as confirmed by the prior art:

> 8. Regeneron Pharmaceuticals Inc. Regeneron Reports Second Quarter Financial and Operating Results; BLA Filing for Auto-Inflammatory Diseases Planned for Early 2007; Two Antibody Candidates from VelocImmune(R) Program to Enter Clinical Trials Each Year Beginning in 2007. Media Release: 3 Aug 2006. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added); *see also id.* (Ref. Nos. 6, 18)).

101. Second, in my opinion, a person of ordinary skill in the art would have been aware of such company filings, such as Regeneron's September 30, 2009 10-Q ("2009 10-Q") (Ex.1021, 2009 10-Q), and would routinely look to 10-Q filings to determine what drugs and treatments pharmaceutical companies were working on. Here, Regeneron disclosed information regarding, among other things, its ongoing development of the VEGF Trap-Eye program—specifically focused on the clinical trials for VEGF Trap-Eye—in its September 30, 2009 10-Q. (Ex.1021, 2009 10-Q, 20 ("The VIEW 1 and VIEW 2 trials are both evaluating VEGF Trap-Eye doses of

. . . 2.0 mg at a dosing interval of eight weeks (after three monthly doses).")). 2009 10-Q also disclosed results of the CLEAR-IT trial, which included "monthly doses of VEGF Trap-Eye of . . . 2.0 . . . mg for 12 weeks followed by PRN dosing," and the DA VINCI trial. (*Id.*, 19-20).

102. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in 2009 10-Q included the experimental groups that received VEGF Trap-Eye 2.0 mg every eight weeks following three monthly "loading dose" injections or "monthly doses of VEGF Trap-Eye of . . . 2.0 . . . mg for 12 weeks followed by PRN dosing." (Ex.1021, 2009 10-Q, 19-20).

103. Thus, in my opinion, a person of ordinary skill in the art also would have been interested in, and sought out, the information disclosed in 2009 10-Q because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with angiogenic eye disorders such as wet AMD. (Ex.1021, 2009 10-Q, 19-20). My opinion in this regard is confirmed by other contemporaneous prior art to the '069 patent which expressly refer to the Regeneron 2010 Financial Press Release which, in turn, directed a person of ordinary skill in the art to Regeneron's company filings with the SEC. (*See* Ex.1007, Adis, 268 (Ref. Nos. 6, 18)). Indeed, company filings such as 2009 10-Q were well known—and widely available—to the community

interested in the subject matter of the '069 patent. (*See id.*, 262-63, 268 (Reference Nos. 6, 18)).

104. It is also my opinion that 2009 10-Q would have been routinely available to a person of ordinary skill in the art. Prior to 2011, a person of ordinary skill in the art would have been able to locate 2009 10-Q exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[25] Thus, a person of ordinary skill in the art could have easily accessed 2009 10-Q via Regeneron's website and easily downloaded an electronic copy.

105. For at least these reasons, it is my opinion that 2009 10-Q was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '069 patent, exercising reasonable diligence, before 2011.

## IX. CONCLUDING STATEMENTS.

106. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the USPTO Patent Trial and Appeal Board. I

[25] *See* Ex.1021, 2009 10-Q.

acknowledge that I may be subject to cross-examination in this case. If cross-examination is required of me, I will appear for cross-examination during the time allotted for such cross-examination.

107. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: April 30, 2021

Mary Gerritsen, Ph.D.

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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*Inter Partes* Review No.: IPR2021-00881

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

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

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

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| 1002 | Expert Declaration of Dr. Thomas A. Albini in Support of Petition for *Inter Partes* Review of Patent No. 9,254,338 B2, dated May 4, 2021 ("Albini") |
| 1003 | Expert Declaration of Mary Gerritsen, Ph.D. in Support of Petition for *Inter Partes* Review of U.S. Patent No. 9,254,338 B2, dated Apr. 26, 2021 ("Gerritsen") |
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| 1093 | Amino acid sequence alignment of SEQ ID NO:2 of the '338 patent with SEQ ID NO:16 of the '758 patent and SEQ ID NO:4 of Dix ("'338 Amino Acid Sequences") |
| 1094 | Nucleotide sequence alignment of SEQ ID NO:1 of the '338 patent with SEQ ID NO:15 of the '758 patent and SEQ ID NO:3 of Dix ("'338 Nucleotide Sequences") |

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

## I. INTRODUCTION.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### C. Lead and Back-Up Counsel and Service Information (37 C.F.R. § 42.8(b)(3)-(4)).

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

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

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

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

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

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

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

## V. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW.

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

## VI. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED.

### A. CHALLENGED CLAIMS.

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

### B. STATUTORY GROUNDS OF CHALLENGE.

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

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

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

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

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

## VII. OVERVIEW OF THE '338 PATENT.

### A. THE '338 PATENT.[1]

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

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

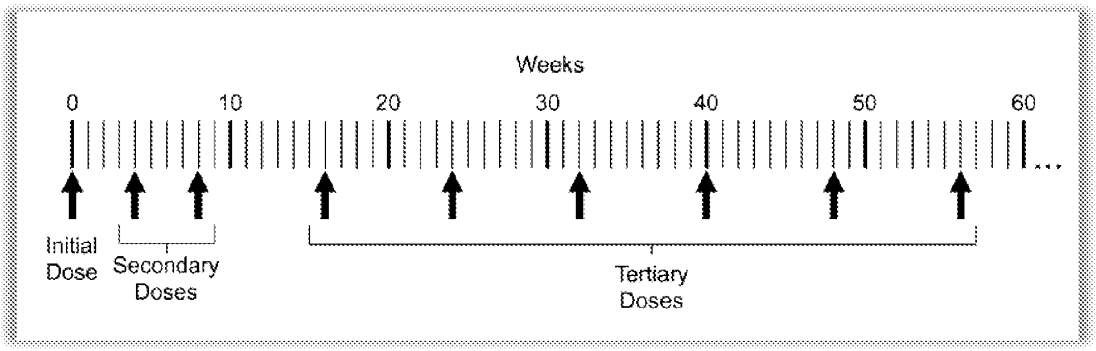
[2] Vascular endothelial growth factor (VEGF) is a "naturally occurring glycoprotein in the body that acts as a growth factor for endothelial cells." (Ex.1011, Semeraro, 711). Early research linked activity of VEGF-A to the development of ocular diseases such as neovascular AMD. (Ex.1043, Brown, 627-28).

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

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

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

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




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

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

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

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

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

### B. EUROPEAN EQUIVALENT, EP-325.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

---

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

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

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

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

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

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

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

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

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

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

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

### D. "TREATING."

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## IX. PERSON OF ORDINARY SKILL IN THE ART.

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

## X. THE SCOPE AND CONTENT OF THE PRIOR ART.

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

### A. VEGF TRAP-EYE/AFLIBERCEPT BACKGROUND.

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

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

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

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

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

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

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

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

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

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

**1. Dixon (Ex.1006).**

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

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Regeneron Press Releases)).

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

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

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

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

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

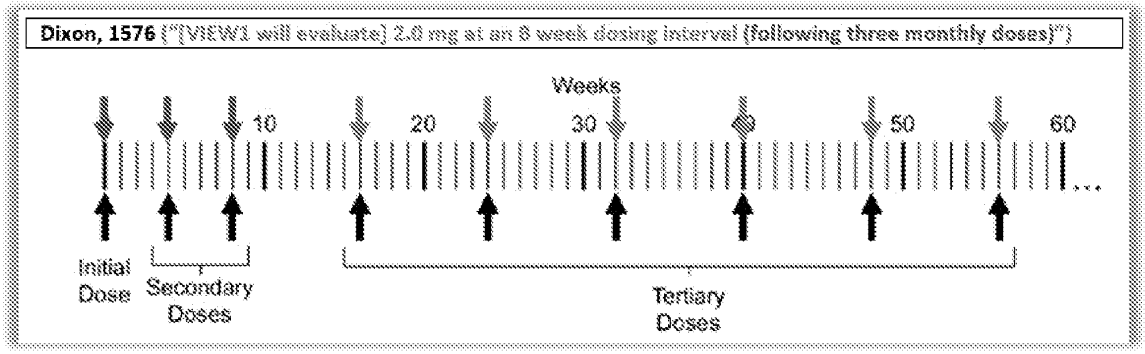


**Figure 1.** (Modified from Fig.1 of the '338 patent).

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

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

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

**2. Adis (Ex.1007).**

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

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

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

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

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

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

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

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

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

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

**4. NCT-795 (Ex.1014).**

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

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

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

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

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

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

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

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

**5. NCT-377 (Ex.1015).**

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

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

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

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

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

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

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

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

**7. Dix (Ex.1033).**

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

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

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

## XI. GROUNDS FOR UNPATENTABILITY—DETAILED ANALYSIS.

### A. ANTICIPATION.

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

**1. Legal standards.**

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

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

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

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

### 2. Ground 1: Dixon anticipates the Challenged Claims.

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

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

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

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

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

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

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

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

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

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

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

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[10] *See supra* n.11.

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

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

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

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

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

### 3. Ground 2: Adis anticipates the Challenged Claims.

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

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

200), discloses each and every element:

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

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

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

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

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

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

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

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

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

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

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

discloses the additional limitations, and thus anticipates.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* * *

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

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

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

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

**B. Obviousness.**

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

**1. Legal standard.**

A patent claim is invalid under 35 U.S.C. § 103(a) if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *KSR*, 550 U.S. at 406. Furthermore, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it

is likely the product not of innovation but of ordinary skill and common sense." *Id.* at 421.

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

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

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

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

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

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

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

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

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

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

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

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

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

**3. No secondary considerations.**

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

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

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

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

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

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

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

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

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

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

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

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

## XII. CONCLUSION.

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

Dated: May 5, 2021

Respectfully Submitted,

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## CERTIFICATE OF SERVICE

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

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

## CERTIFICATE OF COMPLIANCE

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

Dated: May 5, 2021

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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

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# PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.

US 169985497v27

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## TABLE OF EXHIBITS

| Ex. No. | Description |
|---|---|
| 2001 | Expert Declaration of Dr. Diana V. Do, M.D. |
| 2002 | Curriculum Vitae of Dr. Diana Do |
| 2003 | Lucentis (ranibzumab injection) label, revised June 2010 |
| 2004 | Ex. (a)(1)(a) to Tender Offer Statement to Momenta, filed with SEC on September 2, 2020 |
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| 2007 | Press Release, THOMAS REUTERS INTEGRITY "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting" (September 2008) |
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| 2020 | A Study Investigating the Safety and Efficacy of Lampalizumab Intravitreal Injections in Participants With Geographic Atrophy Secondary to Age-Related Macular Degeneration (SPECTRI), NCT02247531, ClinicalTrials.gov (August 2, 2021), https://clinicaltrials.gov/ct2/show/NCT02247531?term=lampalizumab&phase=2&draw=2&rank=2 |
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| 2039 | Press Release, *Regeneron, Regeneron Reports Fourth Quarter and Full Year 2012 Financial and Operating Results*, dated February 14, 2013 |
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| 2041 | Press Release, Regeneron, *Regeneron and Bayer Report Positive Results for VEGF Trap-Eye in Phase 3 Study in Central Retinal Vein Occlusion (CRVO) and in Phase 2 Study in Diabetic Macular Edema (DME)*, dated December 20, 2010 |
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Regeneron Pharmaceuticals, Inc. ("Patent Owner" or "Regeneron") submits this preliminary response pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107 to Mylan Pharmaceuticals Inc.'s ("Petitioner's" or "MPI's") request for *inter partes* review ("IPR") of 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).

## I. INTRODUCTION

Petitioner is developing a biosimilar of EYLEA® and files this challenge to invalidate Regeneron's '338 Patent, which covers the FDA-recommended dosing regimen for EYLEA®. Petitioner's challenge relies entirely on references disclosing the design of Regeneron's Phase 3 trials. But Petitioner fundamentally ignores that there existed great uncertainty as to whether an extended, fixed dosing regimen (Q8) would work until Regeneron's Phase 3 clinical trial results showed that it could. Petitioner also ignores that this same prospective dosing regimen was before the Examiner during prosecution of the '338 Patent.

Before EYLEA®, the standard of care for treating angiogenic eye disorders was monthly intravitreal injections of ranibizumab (Lucentis®), an antibody fragment that binds Vascular Endothelial Growth Factor ("VEGF"), or monthly off-label use of bevacizumab (Avastin®), an anti-VEGF antibody. The great burden of monthly intravitreal injections led to several attempts to decrease the frequency of injections and physician monitoring. Ex. 1018, 1, and 9-10. However, existing VEGF inhibitors were ineffective at maintaining vision when

dosed on a fixed quarterly basis or on an "as-needed" (*pro re nata*) basis without monthly monitoring visits. Ex. 1018, 10; Ex. 1001, 1:55-59; Ex. 2003, 5. Indeed, before the results of Regeneron's pivotal Phase 3 trials, no one had demonstrated that a longer-than-monthly fixed dosing regimen (*e.g.*, eight weeks or longer) could maintain, let alone improve, vision.

Regeneron's Phase 3 clinical trial results surprisingly demonstrated that "remarkably similar improvement in vision and anatomic measures can be achieved" with less frequent EYLEA® dosing as compared to monthly ranibizumab injections. Ex. 1018, 10. Having secured the data necessary to support the eight-week extended dosing regimen of the instant claims, Regeneron obtained FDA approval for EYLEA® and was awarded the '338 Patent covering its recommended dosing regimen. EYLEA®'s duration and ability to extend the time between injections has made it a life-changing drug and revolutionized the treatment of angiogenic eye disorders. Given the long-felt need and repeated failures of others to reduce treatment burden and injection frequency, EYLEA® has enjoyed great commercial success.

The Petition should be denied for at least the following reasons:

***First***, Petitioner flouts the Board's rules by circumventing word count limits and also by disregarding the particularity requirement of 35 U.S.C. § 312(A)(3), presenting "catch-all" obviousness arguments that do not differentiate between seven references and fifteen obviousness theories.

***Second,*** Petitioner's challenges rely on substantially the same art that was previously before the U.S. Patent & Trademark Office ("Office") and considered by the Examiner, yet Petitioner does not allege that the Examiner erred in a manner material to the patentability of the Challenged Claims, warranting discretionary denial under 35 U.S.C. §§ 325(d) and 314(a).

***Third***, Petitioner fails to demonstrate that its cited references expressly or inherently disclose the amino acid or nucleic acid sequence limitations of the Challenged Claims. Petitioner argues that its cited art inherently discloses aflibercept and its amino acid and nucleic acid sequences through reference to "VEGF Trap-Eye." But Petitioner relies on inference to connect "VEGF Trap-Eye" and "aflibercept" that the prior art does not support, and the Federal Circuit has repeatedly held that probabilities are insufficient for anticipation.

***Fourth***, Petitioner's anticipation challenges also rely on an erroneous claim construction that seeks to eliminate the efficacy requirements of the Challenged Claims and Petitioner never shows that the "method of treating" and "tertiary dose" limitations, which require efficacy, are disclosed either expressly or inherently in its cited references.

***Fifth***, Petitioner relies on Regeneron's Phase 2 clinical trial results for its obviousness challenge. But that trial tested a different dosing regimen from that claimed in the '338 Patent and failed to provide the skilled artisan with ***any*** expectation of success — let alone a reasonable one — in practicing the claimed

inventions. In fact, those clinical trial results showed just the opposite —that it was not expected that VEGF Trap-Eye would be effective if dosed at eight-week intervals. Petitioner also ignores that before the priority date, no one, including Regeneron, had ever shown that a fixed eight-week (or longer) dosing regimen could maintain, let alone improve, vision.

## II. THE PETITION SHOULD BE REJECTED FOR CIRCUMVENTING THE WORD LIMIT AND OBFUSCATING ITS GROUNDS

### A. The Petition Violates the Word Limit

The Petition exceeds the 14,000-word limit (37 C.F.R. § 42.24(a)(1)(i)). Despite certifying that the word count for its petition is 13,904 words (Pet., Cert. of Compliance), the Petition's word count includes only the typed words of the Petition. The word count ignores words in images of text from the '338 Patent specification, including a lengthy passage of text on which Petitioner substantively relies for its arguments. *See e.g.*, Pet., 12; *see also* Pet., 9, 29. In total, Petitioner fails to account for 224 words in text images in the Petition which, when included, results in a word count of 14,128 words. Petitioner, thus, disregards the Board's rules, as evidenced by Petitioner's use of the same tactic in its Petition filed in IPR2021-00880. Paper 1. This is a reason to deny institution. Trial Practice Guide (November 2019) at 40 ("Excessive words in figures, drawings, or images, deleting spacing between words, or using excessive acronyms or abbreviations for word phrases, in order to circumvent the rules on

word count, may lead to a party's brief not being considered."); *see Pi-Net Int'l, Inc. v. JPMorgan Chase & Co.*, 600 F. App'x 774 (Fed. Cir. 2015) (denying request to file a corrected brief and dismissing appeal because appellant violated word count).

The proper remedy here is to deny institution, thereby allowing Petitioner to refile a petition that properly conforms with the Board's word count rules. No time bar precludes Petitioner from refiling a petition challenging the '338 Patent.

**B. The Petition Fails the Particularity Requirement**

Despite exceeding the allowed word count, Petitioner still has not managed to state, with particularity, the grounds on which the challenge to each claim is based. Accordingly, the Petition presents an inefficient use of the Board's time and resources, as well as procedural unfairness to Regeneron.

A petition "may be considered only if . . . the petition identifies, in writing and with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim." 35 U.S.C. § 312(a)(3); *see also Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Paper 20 at 15-24 (Mar. 6, 2019) (informative). "[T]he Board may consider whether a lack of particularity as to one or more of the asserted grounds justifies denial of an entire petition." *Id.* at 17. Furthermore, the Office Patent Trial Practice Guide advises practitioners to "focus on concise, well-organized, easy-to-follow arguments supported by readily identifiable evidence of

record." 77 Fed. Reg. 48756, 48763 (August 14, 2012).

Here, Petitioner does not satisfy the particularity requirements under § 312(a)(3) for at least Ground 6 because the Petition suffers from the same deficiencies identified by the Board in *Adaptics*. Specifically, Ground 6 is a "catch-all" ground that alleges that the Challenged Claims are obvious over seven references under fifteen different theories:

1. Dixon;
2. Dixon + the '758 Patent;
3. Dixon + Dix;
4. Adis;
5. Adis + the '758 Patent;
6. Adis + Dix;
7. Regeneron (8-May-2008);
8. Regeneron (8-May-2008) + the '758 Patent;
9. Regeneron (8-May-2008) + Dix;
10. NCT-795;
11. NCT-795 + the '758 Patent;
12. NCT-795 + Dix;
13. NCT-377;
14. NCT-377 + the '758 Patent;

15.NCT-377 + Dix.

See Pet., 62.

Petitioner asserts that five references (Dixon, Adis, Regeneron (8-May-2008), NCT-795, and NCT-377) are interchangeable. Id. at 62 n.12. Petitioner does not explain why all five are necessary for this obviousness ground, nor how each combination differs from the others. Rather, these five references are cited for the disclosure of the same alleged feature. This is at odds with the Office's direction to "avoid submitting a repository of all the information that a judge could possibly consider," and inundates the Board with excessive references for its consideration. 77 Fed. Reg. at 48763.

Furthermore, Petitioner only addresses Dixon in Ground 6 and relegates the other four primary references and fifteen different obviousness theories to a footnote. Pet., 62 n.12. This leaves the Board and Regeneron to fill in the gaps of the Petition. Regeneron is at an unfair disadvantage of having to guess which theories Petitioner will pursue, what evidence allegedly supports those theories, and what purported motivations and reasonable expectation of success Petitioner might advance were trial instituted.

As each theory constitutes a distinct ground, Petitioner impermissibly shifts the burden to the Board and Regeneron to understand the multiplicity of obviousness grounds presented. For at least the reasons above, Regeneron respectfully requests denial of the petition under 35 U.S.C. § 314(a).

### C. Janssen Pharmaceuticals, Inc. Is a Real Party-in-Interest

Petitioner also fails to identify the correct RPIs in its Petition. Petitioner identifies Viatris Inc., Mylan Inc., Mylan Pharmaceuticals Inc., Momenta Pharmaceuticals, Inc., and Johnson & Johnson as real parties-in-interest to the instant Petition. Pet., 4. Petitioner states "[n]o other parties exercised or could have exercised control over this Petition; no other parties funded, directed and controlled this Petition." *Id.* However, Regeneron understands from publicly available documents that Janssen Pharmaceuticals, Inc. ("Janssen") is a real party-in-interest for the same reasons Mylan disclosed these other entities. Multiple Johnson & Johnson press releases and Securities Exchange Commission filings indicate that Janssen, a pharmaceutical company headquartered in Beerse, Belgium, and owned by Johnson & Johnson, is managing the business and operations of Momenta, generally, and the acquired Momenta pipeline of clinical and pre-clinical assets, including a biosimilar to EYLEA®. Ex. 2004, 46 ("the business and operations of Momenta will be managed as one of the Janssen Pharmaceuticals Companies of Johnson & Johnson."); *see also* Ex. 2005; Ex. 2006.

While denial of institution is warranted here, if the Board grants institution, it should require Petitioner to file updated mandatory disclosures identifying Janssen as a real party-in-interest.

## III. THE BOARD SHOULD DENY INSTITUTION UNDER 35 U.S.C. § 325(D)

The Board should exercise its discretion and deny institution under 35 U.S.C. § 325(d) because Petitioner relies on substantially the same art that was already considered by the Examiner during prosecution of the '338 Patent, and fails to argue that the Examiner made any error material to the patentability of the Challenged Claims in considering that art.

### A. Petitioner Mischaracterizes the Prosecution History of the '338 Patent and its Foreign Counterpart

Petitioner repeatedly and baselessly attempts to cast doubt on Regeneron's candor with the Office. Specifically, Petitioner incorrectly asserts that "***none*** of the numerous pre-2011 publications disclosing the VIEW1/VIEW2 dosing regimens . . . were submitted to or cited by the Examiner during prosecution." Pet., 27. This is incorrect. To the contrary, Regeneron's VIEW1/2 dosing regimens were before the Examiner and considered during prosecution of the '338 Patent. On October 18, 2013, Regeneron presented a September 28, 2008, Regeneron Press Release ("9/28/2008 Press Release") to the Office in an IDS, which was marked considered by the Examiner. Ex. 1017, 60 and 277. The 9/28/2008 Press Release discloses the same VIEW1/2 prospective dosing regimen that Petitioner relies on in Grounds 1-5 of its Petition. Ex. 2007, 1; *see* Section III.B, *infra*.

In addition, Petitioner asserts that Regeneron never cited art from EP-325 (the European counterpart to the '338 Patent) to the Examiner of the '338 Patent

and suggests that this was the reason the '338 Patent issued, where its European counterpart did not. Pet., 11. This is also false.

With only one exception[1], all of the art cited in EP-325 was submitted to the Office and considered by the Examiner in the prosecution of the '338 Patent or applications that continued therefrom. Petitioner insinuates that Regeneron hid art cited in third-party observations in EP-325 from the Office, but omits that the third-party observations were not filed with the EPO until seven months ***after*** the '338 Patent issued. Ex. 1063, 214-371; 372-391. Even so, Regeneron submitted the art cited in these third-party observations with the Office in continuing prosecution in multiple applications of the same family, all of which were examined and allowed over such art. Moreover, Petitioner also ignores that the EPO relied on ***disclosure of the clinical trial results*** from Regeneron's Phase 3 VIEW 1/2 trials, less than a year before patent filing, to challenge novelty in EP-325. Ex. 1063, 606-607. However, under U.S. Patent Law, such disclosure is not

[1] Annex 4, a November 30, 2010, ClinicalTrials.gov archive of the VIEW 2 Study, is the only third party-cited reference that does not appear on an IDS submitted during prosecution of Patent No. 9,669,069. Ex. 1063, 665-668. Annex 4 is § 102(a) art and is cumulative of a March 2008 VIEW 2 archive that was submitted during prosecution of the '069 Patent, which issued from a continuation from the '338 Patent. Ex. 2008.

a bar to novelty, and all such disclosures were before the Office in continuing prosecution. Thus, not only were references related to VIEW1/VIEW2 dosing regimen provided to the Office, but the Examiner fully considered those disclosures in allowing the '338 Patent.

### B. Because the Examiner Considered Substantially the Same Art and Petitioner Does Not Allege Any Error, Institution Should Be Denied

The Board applies a two-part framework to analyze discretionary denial under § 325(d): "(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, 2020 WL 740292, at *3-4 (Feb. 13, 2020) (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (Dec. 15, 2017)).

#### 1. The Examiner Considered Substantially the Same Art (*Becton, Dickinson* Factors (a), (b), and (d))

The art relied upon in Petitioner's Grounds is substantially the same as the art presented to, and considered by, the Examiner during '338 Patent prosecution, thus satisfying step one of the *Advanced Bionics* framework.

### a. Grounds 1-5

Central to Petitioner's Grounds 1-5 is that Dixon, Adis, the 5/8/08 Press Release, NCT-795, and NCT-377 each purportedly discloses the prospective VIEW1/2 dosing regimen. Pet., 27-36.

As discussed above, Regeneron presented a 9/28/2008 Press Release to the Office in an IDS during prosecution of the '338 Patent, which was marked considered by the Examiner. Ex. 1017, 60 and 277; Ex. 2007. As shown below, the 9/28/08 Press Release discloses the same VIEW1/2 prospective dosing regimen that Petitioner relies on in its Grounds 1-5. Ex. 2007, 1. Dixon, Adis,[2] the 5/8/08 Press Release, NCT-795, and NCT-377 are essentially identical to the disclosure of the 9/28/08 Press Release:

[2] While Adis discloses the administration of aflibercept, not VEGF Trap-Eye, (Ex. 1007, 263), Petitioner's anticipation arguments purport that the POSA would have understood "aflibercept" and "VEGF Trap-Eye" to be synonymous. Pet., 23. Therefore, according to Petitioner's characterization of aflibercept and "VEGF Trap-Eye," Adis contains essentially the same disclosure as the 9/28/08 Press Release.

| **9/28/08 Press Release (Ex. 2007, 1)** | **Dixon (Ex. 1006, 1576)** | **Adis (Ex. 1007, 263)** | **5/8/08 Press Release (Ex. 1013)** | **NCT-795 & NCT-377 (Ex. 1014, 8; Ex. 1015, 6)** |
|---|---|---|---|---|
| "In [VIEW1/2], … VEGF Trap-Eye [will be] dosed 0.5 mg every 4 weeks, 2 mg every 4 weeks, **or 2 mg every 8 weeks (following three monthly doses)**…." | "[Phase 3] will evaluate the safety and efficacy of VEGF Trap-Eye at doses of. . . **2.0 mg at an 8 week dosing interval (following three monthly doses)**." | "The non-inferiority, [VIEW1] . . . study will evaluate the safety and efficacy of intravitreal aflibercept at . . . **2.0 mg at an 8-week dosing interval** . . . ." | VIEW2 "will evaluate the safety and efficacy of VEGF Trap-Eye at . . . **2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four.**" | "**2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4)** during the first year." |

The Board has found that substantially the same prior art was previously presented to the Office when the asserted references are cumulative of references provided to the Examiner in an IDS. *NXP USA, Inc. v. Impinj, Inc.*, IPR2020-00519, 2020 WL 4805424, at *3-5 (Aug. 17, 2020); *Gardner Denver, Inc. v. Utex Indus., Inc.*, IPR2020-00333, 2020 WL 4529832, at *5 (Aug. 5, 2020). Thus, the Office was presented with art that was "substantially the same as" Dixon, Adis, the 5/8/08 Press Release, NCT-795, and NCT-377 because Petitioner's use of each is cumulative of the 9/28/08 Press Release.

Petitioner has not identified any material differences between the asserted art and the 9/28/08 Press Release. When a petitioner fails to identify any specific

differences between the asserted art and previously considered art, the Board has properly concluded that the asserted art is cumulative of art that was previously submitted to the Office. *See NXP USA*, 2020 WL 4805424, at *4-5.

**b. Ground 6**

In Ground 6, Petitioner argues that Dixon's disclosure of "positive Phase II trial data," *i.e.*, the results of Regeneron's CLEAR-IT 2 trial, would have provided the POSA with a reasonable expectation of success. Pet., 64. However, as shown below, the 9/28/08 Press Release that Regeneron disclosed to the Office in an IDS discloses the same CLEAR-IT 2 clinical trial results as Dixon:

| **9/28/08 Press Release (Ex. 2007, 1)** | **Dixon (Ex. 1006, 1576)** |
|---|---|
| "Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12)." | "Two groups initially received monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye (at weeks 0, 4, 8, and 12) and three groups received quarterly doses of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye (at baseline and week 12)." |

In addition, Petitioner argues that the '758 Patent (Ex. 1010) and Dix (Ex. 1033) each purportedly "disclose[] the VEGF Trap-Eye sequence and domain architecture." Pet., 63. But substantially the same disclosures as set forth in both of those references were presented to the Examiner during prosecution of the '338 Patent.

When a continuation-in-part of an asserted reference (1) includes the same disclosure as the disclosure in the asserted reference upon which the Petitioner

relies, and (2) was provided to the Examiner in an IDS, the Board has determined that substantially the same reference was presented to the Office. *Boragen, Inc. v. Syngenta Participations AG*, IPR2020-00124, 2020 WL 2206972, at *8 (May 5, 2020). Here, Regeneron provided a continuation-in-part of the '758 Patent, U.S. Patent App. No. 2006/0058234 (Ex. 2009) ("the '234 Application"), to the Office in an IDS, and the Examiner marked it considered during prosecution. Ex. 1017, 66 and 112. The '234 Application contains the same amino acid sequence that Petitioner identifies as the VEGF Trap-Eye sequence in the '758 Patent. *Compare* Ex. 2009, SEQ ID No. 7 *with* Ex. 1010, Figs. 24A-C. Accordingly, the '758 Patent is substantially the same as the '234 Application, which was considered by the Examiner during original prosecution.

Likewise, the Dix reference is also cumulative of the '234 Application. Petitioner asserts that Dix discloses the amino acid sequence of "VEGF Trap-Eye." Pet., 63. As noted above, the '234 Application discloses the identical sequence. *Compare* Ex. 2009, SEQ ID NO. 7 *with* Ex. 1033, SEQ ID NO. 3. Thus, although Dix was not previously presented to the Office, it is cumulative of the '234 Application that the Examiner considered during prosecution of the '338 Patent.

Thus, the Office was previously presented with "substantially the same" art as the '758 Patent and Dix. *See e.g., NXP USA*, 2020 WL 4805424, at *4-5.

### 2. Petitioner Fails to Argue that the Examiner Erred in a Manner Material to Patentability (*Becton, Dickinson* Factors (c), (e), and (f))

Because substantially the same art was previously presented to the Office, Petitioner must show that the Office erred in a manner material to the patentability of the Challenged Claims. "An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Advanced Bionics*, 2020 WL 740292, at *3 n.9. "If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability." *Id.* at *3.

Petitioner never once alleges that the Examiner committed any error; indeed, the word "error" does not appear anywhere in the Petition. Nor does Petitioner allege that the Examiner overlooked or misapprehended something during prosecution. The Board has repeatedly determined that failure to allege material error is a sufficient basis to determine that a petitioner did not carry its burden as to step two. *E.g.*, *ABS Global, Inc. v. Cytonome/ST, LLC*, IPR2021-00306, Paper 13 at 13-14 (Jun. 7, 2021) ("[W]here Petitioner has made no allegation of material error beyond the allegation that the Examiner did not apply the [asserted] reference and has not pointed out any specific disclosure from [the asserted reference] that was overlooked by the Office, we agree with Patent Owner that Petitioner fails to demonstrate material error."); *Sony Interactive Ent.*

*LLC v. Terminal Reality, Inc.*, IPR2020-00711, 2020 WL 6065188, at *5 (Oct. 13, 2020) ("Sony [Petitioner] was provided the opportunity to provide explanation [of material error], but Sony was silent in this regard.... Accordingly, *Becton, Dickinson* Factor (e) favors exercising our discretion to deny institution.").

Because substantially the same art was previously presented to the Office and was considered by the Examiner, and Petitioner fails to demonstrate that the Examiner committed an error material to the patentability of the Challenged Claims, the Board should exercise its discretion and deny institution under § 325(d). *See Dynatemp Int'l, Inc. v. R 421A LLC d/b/a Choice Refrigerants*, IPR2020-01660, Paper 15, 20-26 (Apr. 20, 2021) (institution denied where seven of eight asserted references were cumulative of previously presented reference and petitioner did not identify or sufficiently explain material error).

## IV. THE BOARD SHOULD DENY INSTITUTION BECAUSE PETITIONER FAILS TO MAKE ITS THRESHOLD SHOWING THAT AT LEAST ONE CHALLENGED CLAIM IS UNPATENTABLE

For the reasons discussed below, Petitioner fails to "demonstrate that there is a reasonable likelihood that at least 1 of the" '338 Patent claims is unpatentable for Grounds 1 through 6, and thus, denial of the petition is warranted. 35 U.S.C. § 314(a).

### A. Grounds 1, 3-5: Petitioner Fails to Demonstrate that "VEGF Trap-Eye" Was Known in the Art to Correspond to SEQ ID NO: 2 or SEQ ID NO:1

Petitioner asserts that Dixon (Ground 1), Regeneron (8-May-2008) (Ground 3), NCT-795 (Ground 4) and NCT-377 (Ground 5) anticipate the Challenged Claims. Anticipation requires "each and every claim limitation [to 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).

Petitioner's anticipation argument relies on its unproven assumption that "VEGF Trap-Eye" was known in the art to possess the same amino acid sequence as aflibercept. However, none of Petitioner's cited references discloses the amino acid sequence of "VEGF Trap-Eye." To show inherent anticipation of the amino acid and nucleic acid limitations of claims 1 and 14, respectively, Petitioner must establish that the amino acid sequence of "VEGF Trap-Eye" was known to be the same as the amino acid sequence of aflibercept. Petitioner's anticipation argument should be rejected because Petitioner fails to establish that "VEGF Trap-Eye" was known in the art to have the amino acid sequence of SEQ ID NO:2 or be encoded by the nucleic acid sequence of SEQ ID NO:1.

#### 1. Petitioner Fails to Establish that "VEGF Trap-Eye" Was Known in the Art to Comprise SEQ ID NO: 2 (Claims 1, 3-11, and 13)

Claim 1 and its dependent claims require the administration of a VEGF antagonist comprising amino acids 27-457 of SEQ ID NO:2. Ex. 1001, 23:12-17.

Since none of the cited references disclose any sequence information for "VEGF Trap-Eye," Petitioner argues that the "express disclosure of VEGF Trap-Eye thus anticipates," because "amino acid and structural information for VEGF Trap-Eye … was well-known and widely published to skilled artisans." Pet., 40-41.

But Petitioner has not identified ***any*** prior art that disclosed the amino acid sequence or nucleic acid sequence for "VEGF Trap-Eye." Specifically, Grounds 1 and 3-5 rely on Dixon, Regeneron (8-May-2008), NCT-795 and NCT-377, respectively. The full extent of Dixon's disclosure regarding "VEGF Trap-Eye" is that "VEGF Trap-Eye" is "a fusion protein of binding domains of VEGF receptors-1 and -2 attached the Fc fragment of human IgG." Ex. 1006, 1576. Nothing more is provided that would allow the POSA to differentiate Dixon's "VEGF Trap-Eye" from any other proteins comprising an hVEGF-R1 domain 2, hVEGF-R2 domain 3, and a human Fc region. Notably, Dixon does not specify which amino acids of the VEGF receptor-1 or receptor-2 domains comprise "VEGF Trap-Eye." Dixon also does not say that "VEGF Trap-Eye" and aflibercept have the same amino acid sequence, but only that "VEGF Trap-Eye" and aflibercept (the oncology product) share a "molecular structure." Ex. 1006, 1575. As explained below, this is not a disclosure of VEGF Trap-Eye's amino acid sequence.

Regeneron (8-May-2008) reports on the initiation of VIEW1/2 clinical trials for "evaluating VEGF Trap-Eye for the treatment of the neovascular from of Age-

related Macular Degeneration (wet AMD)." Ex. 1013, 1. Regeneron (8-May-2008) refers exclusively to administration of "VEGF Trap-Eye" and provides only that "VEGF Trap-Eye" "is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related placental growth factor (PlGF) and VEGF-B." *Id.* at 2. This reference thus does not disclose an amino acid sequence for VEGF Trap-Eye.

NCT-795 and NCT-377 reflect historical changes for VIEW1/2 clinical trials as posted on clinicaltrials.gov. Ex. 1014, 3; Ex. 1015, 3. Both NCT-795 and NCT-377 state that "2.0 mg ***VEGF Trap-Eye*** [was] administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." Ex. 1014, 8; Ex. 1015, 6 (emphasis added). Neither NCT-795 nor NCT-377 provides any information regarding the amino acid sequence of "VEGF Trap" or "VEGF Trap-Eye."

Based largely on Dixon's disclosure that "VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure," Petitioner argues that "VEGF Trap-Eye" would be understood to refer to aflibercept — and to only aflibercept — and that aflibercept's amino acid sequence was well-known. Pet., 40-41 (quoting Ex. 1006, 1576-1575). However, Petitioner ignores evidence that the POSA would ***not*** have understood that VEGF Trap-Eye and aflibercept ***necessarily*** have the same amino acid sequence, such as the evidence discussed below showing different reported molecular weights for VEGF Trap-Eye and

aflibercept, and inconsistent descriptions of "VEGF Trap," "VEGF Trap-Eye" and "aflibercept" in the art. Consequently, Petitioner fails to satisfy its burden to show that, as of January 2011, the POSA would have known that the amino acid sequence of "VEGF Trap-Eye" was necessarily the same as the amino acid sequence of aflibercept and, as a result, that SEQ ID NO:2 was inherently disclosed by Dixon.

Petitioner's burden to show inherent anticipation is exacting, and Petitioner does not come close to meeting it here. The prior art's use of the term "VEGF Trap-Eye" was inconsistent, and Petitioner fails to show a clear or uniform understanding that "VEGF Trap-Eye" was just another name for "aflibercept" in the art. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is ***necessarily present*** … and that it would be so recognized by persons of ordinary skill.") (emphasis added).

**a. Petitioner and Its Expert Repeatedly Equate "Aflibercept" with All Variations of "VEGF Trap"**

Petitioner relies on the disclosure of "VEGF Trap-Eye" as anticipating the claimed sequence information, but as shown above, identifies no amino acid sequence information for "VEGF Trap-Eye."

Petitioner relies heavily on a statement in Dixon that "VEGF Trap-Eye" and aflibercept (the oncology product) share a "molecular structure." Ex. 1006, 1575. But Dixon does not state that "VEGF Trap-Eye" and aflibercept have an identical

amino acid sequence. And Petitioner provides no evidence that the POSA would understand a shared "molecular structure" to indicate an identical amino acid sequence.[3] Indeed, in the immediately preceding paragraph, Dixon discloses 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, 1575. Dixon's 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. *Id.* at 1576. Thus, Dixon itself suggests that the "molecular structure" of VEGF Trap-Eye may refer to a more general selection and arrangement of receptor binding domains and an Fc region, not a precise amino acid, or nucleic acid sequence.

Given the absence of any sequence disclosure in Dixon, Petitioner tries to connect the dots by arguing that "VEGF Trap-Eye" and aflibercept were different names for the very same protein: "Aflibercept, VEGF Trap, VEGF Trap-Eye, VEGF-Trap$_{R1R2}$, and AVE0005 are simply different names for the ***same molecule***." Pet., 23 (emphasis added); Ex. 1002, ¶18. However, by equating

[3] A protein molecule has multiple levels of "structure": primary (the amino acid sequence), secondary (spatial arrangement of adjacent amino acid residues), tertiary (overall three-dimensional structure), and quaternary (arrangement of several protein chains or subunits). Ex. 2010, 15-16.

"VEGF Trap Eye" with all variations of "VEGF Trap" nomenclature, including VEGF Trap names that were known in the art to refer to a genus of proteins, Petitioner and Dr. Albini only underscore the uncertainty confronting the POSA regarding the identity and sequence of "VEGF Trap-Eye."

Not only does Petitioner fail to meet its burden, but it also fails to consider evidence that would signal to the POSA that "VEGF Trap-Eye" was used to describe many different fusion proteins. For example, "VEGF Trap" was known in the art to encompass a genus of engineered fusion proteins, each having a different amino acid sequence. Holash 2002 *et al.* describes several different Regeneron-developed VEGF-Traps (*e.g.*, VEGF $Trap_{parental}$, VEGF-$Trap_{\Delta B1}$, VEGF-$Trap_{\Delta B2}$, VEGF $Trap_{R1R2}$). Ex. 1004, 11394. Notably, Holash never uses the term "VEGF Trap-Eye" (or aflibercept) for any of the VEGF Trap fusion proteins it describes. And none of VEGF $Trap_{parental}$, VEGF-$Trap_{\Delta B1}$, VEGF-$Trap_{\Delta B2}$ satisfies the sequence limitation of the Challenged Claims. Thus, the POSA would have known of numerous Regeneron "VEGF-Trap" molecules, including many that do not comprise SEQ ID NO:2.

To succeed on its inherency theory, Petitioner must establish that "VEGF Trap-Eye" as disclosed by Dixon and understood by the POSA as of the priority date ***necessarily*** referred to a ***single*** protein (aflibercept) having the amino acid

sequence of SEQ ID NO:2.[4] Yet Petitioner equates "VEGF Trap-Eye" with various names that connoted an entire class of molecules. Petitioner has not and cannot establish that the POSA understood that "VEGF Trap-Eye" ***necessarily*** possessed the same amino acid sequence as aflibercept.

**b. Petitioner Fails to Address Uncertainty in the Art as to the Amino Acid Sequence of "VEGF Trap-Eye"**

As of the priority date, the POSA would have been aware of inconsistent reports in the literature regarding the molecular weight of "VEGF Trap-Eye." For example, a 2009 publication reports that "***VEGF Trap-Eye[24] is a 110-kDa*** recombinant protein," while a 2010 publication reports that "***VEGF Trap-Eye (Regeneron Inc.) is a 115-kDa*** recombinant fusion protein." Ex. 1075, 403; *see*

[4] 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" (Pet., 24), but the meaning of "VEGF Trap-Eye" must be understood as the POSA would view the term as of the priority date without reference to how the term may have later changed. *See Schering 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). Accordingly, the meaning of the term "VEGF Trap-Eye" must encompass all possible molecules to which that term referred as of the priority date.

*also* Ex. 2011, 667 ("VEGF Trap, ***a 110 kDa soluble protein***…."); *cf.* Ex. 2012, 49 and Ex. 2013, 144 ("***VEGF Trap is a 115 kDa*** recombinant fusion protein….") (emphases added).

Conversely, the molecular weight of aflibercept was routinely reported as 115 kDa. *See e.g.*, Ex. 2014, 596 ("…***aflibercept*** is a soluble fusion protein …. Its molecular weight is ***115 kDa***…"); Ex. 2015, [0003] and [0010] (explaining that "VEGF Trap" is a chimeric protein with several embodiments and "has a molecular weight which is substantially less than that of Avastin (***115 kDa for aflibercept*** versus 160 kDa for Avastin)….") (emphases added).

The POSA would have understood that differences in protein molecular weights can reflect differences in the amino acid sequences of the proteins. Specifically, 5,000 Da could equate to a sequence difference of ~42 amino acids (the average molecular weight of an amino acid is ~110-118 Da). Ex. 2016, 1272; Ex. 2017, 11. Thus, in light of a difference of 5,000 Da in the reported molecular weights of "VEGF Trap-Eye," the POSA may have understood the term to refer to a family of fusion proteins with different amino acid sequences having molecular weights in the range of 110-115 kDa. Or the POSA may have understood "VEGF Trap-Eye" to refer to two "VEGF Trap" fusion proteins with different amino acid sequences, one weighing 110 kDa and the other weighing 115 kDa. Or, alternatively, the POSA may have understood "VEGF Trap-Eye" to refer to a single protein amino acid sequence, such as the sequence of aflibercept or that of

another protein the class of VEGF Traps. The Petition, however, is devoid of evidence indicating how the POSA would have understood these varying prior art disclosures regarding the identity of the term "VEGF Trap-Eye."

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 sequence of SEQ ID NO:2. Consequently, Petitioner fails to show that its cited art anticipates claims 1, 3-11, and 13.

### 2. Petitioner Fails to Establish that "VEGF Trap-Eye" Was Known in the Art to Be Encoded by SEQ ID NO:1

Claim 14 and its dependent claims require that the VEGF antagonist is a receptor-based chimeric molecule encoded by the nucleic acid sequence of SEQ ID NO:1. Ex. 1001, 24:13-15. Petitioner argues that "[l]ike the amino acid sequence, the nucleotide sequence for VEGF Trap-Eye was disclosed in the prior art and well known to skilled artisans." Pet., 41 (citing Ex. 1002, ¶¶147-150). Yet, neither the amino acid sequence nor nucleic acid sequence of "VEGF Trap-Eye" is expressly disclosed in Petitioner's cited art. Moreover, because Petitioner fails to establish that "VEGF Trap-Eye" necessarily has the amino acid sequence of aflibercept, it also fails to show that "VEGF Trap-Eye" is necessarily encoded by the nucleic acid sequence of SEQ ID. NO:1.

Petitioner and its expert Dr. Albini argue that "the sequence aspect of clam 14 was widely published in the prior art" based on Dixon (Ex. 1006), the '758

patent (Ex. 1010), Dix (Ex. 1033), and the '095 patent (Ex. 1039).[5] Ex. 1002, ¶149. However, none of these references discloses the nucleic acid sequence of "VEGF Trap-Eye."

Dixon does not disclose any nucleic acid sequence information, let alone the nucleic acid sequence for "VEGF Trap-Eye." Dixon's generic disclosures of "VEGF Trap-Eye" or aflibercept, without correlating those terms to SEQ ID NO:1, is insufficient.

Likewise, Petitioner fails to show that the nucleic acid sequences disclosed in the '758 Patent, Dix, and the '095 Patent were known by the POSA to correspond to either "VEGF Trap-Eye" or "aflibercept." The '758 Patent discloses VEGF-binding construct sequences. Ex. 1010, 10:15-17 ("FIG. 24A-24C. Nucleotide (SEQ ID NO:15) and deduced amino acid sequence (SEQ ID NO:16) of the modified Flt1 receptor termed VEGFR1R2-FcAC1(a)."). But the '758 Patent does not correlate these disclosed nucleic acid sequences to the terms "VEGF Trap-Eye" or "aflibercept." Dix also discloses nucleic acid sequences of "VEGF trap proteins" or "VEGF antagonist" fusion proteins but never identifies these proteins as "VEGF Trap-Eye" or "aflibercept." Ex. 1033, [0013]-[0014], [0030]. Likewise, the '095 Patent never equates any of its

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[5] Dr. Albini also cites to Exs. 1007 and 1021 that do not include any sequence information. Ex. 1002, ¶149.

disclosed nucleic acid sequences with "VEGF Trap-Eye" or "aflibercept."

The mere possibility that "VEGF Trap-Eye" or "aflibercept" could comprise a nucleic acid sequence meeting the limitation of claim 14 is insufficient to demonstrate inherency for anticipation. *See Amgen, Inc. v. Alexion Pharms., Inc.*, IPR2019-00739, Paper 15, at 24-25 (Aug. 30, 2019) (rejecting inherent anticipation where "eculizumab" referred to at least two different proteins in the prior art, including the unclaimed "Thomas IgG4 isotype eculizumab").

### B. Ground 2: Petitioner Fails to Demonstrate that There Is a Reasonable Likelihood that at Least One of the Challenged Clams Is Anticipated by Adis

Petitioner fails to show that there is a reasonable likelihood that at least one Challenged Claim is unpatentable for anticipation based on Adis. 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).

Petitioner relies on two passages in Adis, regarding the prospective VIEW1/2 trials, as disclosing the claimed dosing regimen. Pet., 45-46. For VIEW 1, Petitioner relies on the following passage:

> [S]tudy 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.

This passage does ***not*** disclose the claimed regimen of an initial dose followed by one or more secondary doses 2 to 4 weeks after the preceding dose, followed by tertiary doses every 8 weeks. To be clear, Adis's description of VIEW 1 makes no mention of an initial dose or secondary doses preceding an 8-week dosing interval.

For VIEW 2, Petitioner relies on the following passage:

> 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 (emphasis added).

But Adis's description of VIEW 2 does not specify which of these three study arms receives the "one additional 2.0 mg dose at week 4." Petitioner and its expert use hindsight to interpret this passage to arrive at the claimed regimen. *Janssen Pharms., Inc. v. Watson Lab'ys, Inc.*, C.A. No. 08-5103(SRC), 2012 WL 3990221, at *6-10 (D.N.J. Sept. 11, 2012) ("There is no legal basis for rewriting the prior art to create a hindsight anticipation."). But the language of Adis is unclear, and this passage could be interpreted by the POSA to mean several different possible regimens, including (1) 0.5 mg administered at 4-week dosing intervals with an additional 2.0 mg dose at week 4; (2) 2.0 mg administered at 4-week dosing intervals, with an additional 2.0 mg dose at week 4; or (3) 2.0 mg at

an 8-week dosing interval with an additional 2.0 mg dose at week 4. It is also possible that the POSA would have concluded that Adis's description of VIEW 2, which is inconsistent with Adis's description of the VIEW 1 dosing regimen, was simply incorrect. Consequently, Petitioner fails to show that the disclosures in Adis are arranged as in the Challenged Claims of the '338 Patent.

### C. Grounds 1-5: Petitioner Fails to Establish Any of Its References Disclose a "Method of Treating" and "Tertiary Dose"

None of Petitioner's cited references expressly discloses the required efficacy limitations. Nor could they, as each reference discloses a prospective study that had not yet occurred.[6] *See e.g.*, Ex. 1006, 1576 (The Phase 3 study "***will evaluate*** the safety and efficacy of intravitreal VEGF Trap-Eye at doses of 0.5 and 2.0 mg administered at 4-week dosing intervals and 2.0 mg at an 8 week dosing interval (following three monthly doses)…") (emphasis added).

Unable to show these limitations in the art, Petitioner argues alternatively that: (1) the Challenged Claims require no efficacy; or (2) the required efficacy is inherent to the disclosed prospective dosing regimen. Neither argument succeeds.

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[6] At the time of publication of each reference relied on by Petitioner for anticipation, testing in the VIEW trials was incomplete and the results were unknown. *See, e.g.*, Ex. 1006, 1577.

### 1. Claim Construction

Petitioner's proposed claim construction is so divorced from the '338 Patent's claims, specification, and prosecution history, that it renders the treatment of the "method of treating" claims meaningless. Without the requirement of an efficacious method of treating, as Petitioner proposes, the Challenged Claims would cover administering a VEGF antagonist fusion protein to individuals with any disease, or even no disease at all. It would also cover administering such minute quantities of the fusion protein — in sub-nanogram quantities, for example — that no POSA would understand to constitute a "method of treating."

The claim language and intrinsic record make two things abundantly clear: (1) the claimed methods of treatment are for people suffering from an angiogenic eye disorder; and (2) the claimed dosing regimens were a significant advance over existing therapies because they enabled less frequent dosing while maintaining a high degree of therapeutic efficacy. Petitioner does not dispute either point. Instead, it offers various (erroneous) reasons to ignore this unambiguous intrinsic evidence. For the reasons explained below, Regeneron's constructions should be adopted.[7]

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[7] Petitioner proposes constructions for (1) "4 weeks" and "Pro re Nata (PRN)"; and (2) "VEGFR1 Component," "VEGFR2 Component" and the "Multimerization Component." Pet., 16-17. Regeneron does not advance claim construction positions for these terms because construction of these terms is not necessary to

### a. The Preamble of the Independent Claims Is a Limitation of the Claim

The preamble of claims 1 and 14 — "A method for treating an angiogenic eye disorder in a patient" — is limiting because it (1) imparts meaning to the claims and (2) provides the antecedent basis for the term "patient" in the body of the independent claims and the types of angiogenic eye disorders specified in the body of the dependent claims.

The preamble is not merely a statement of intended results but, as evidenced by the specification, gives life and meaning to the claims. *See, e.g.*, *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002). The preamble sets forth the essence of the claimed invention — "treat[ment] [of] an angiogenic eye disorder in a patient." Ex. 1001, claims 1, 14; *see also* Ex. 1001, Abstract ("The present invention provides methods for treating angiogenic eye disorders …."); *id.* at 2:3-22 (same); *Griffin*, 285 F.3d at 1033 (construing preamble that recites a "method

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resolve the arguments presented in this preliminary response. *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, Petitioner argues that Regeneron "ignores construing 'initial' and 'secondary'" doses. *See* Pet., 15. Because the terms "initial" and "secondary" need not be construed to resolve Petitioner's grounds, it is unnecessary to construe them here. *Nidec*, 868 F.3d at 1017.

for diagnosing" as limiting because "[d]iagnosis is … the essence of th[e] invention; its appearance in the count gives 'life and meaning' to the manipulative steps"). Without limiting the claim to treating patients, the remaining steps of the claim become a meaningless exercise in administering a drug to a person who may have no need whatsoever for the treatment.

The specification confirms what the explicit language of the preamble dictates — that treatment of an angiogenic eye disorder is the entire purpose of the claimed invention: "the invention relates to the administration of VEGF antagonists to ***treat*** eye disorder caused by or associated with angiogenesis. Ex. 1001, 1:18-21 (emphasis added); *see also id.*, 1:63-66 ("The present invention provides methods for ***treating*** angiogenic eye disorders.") (emphasis added), *id.*, 3:19-20 (same), *id.*, 7:15-19 (same). Thus, Petitioner is wrong to assert that "[n]othing in the intrinsic record here suggests" that the preamble is limiting. Pet. 18. To the contrary, the Federal Circuit has routinely held that descriptions of "the present invention" such as these are limiting. *See, e.g.*, *Regents of Univ. of Minn. v. AGA Med. Corp.*, 717 F. 3d 929, 936 (Fed. Cir. 2013); *see also Eon-Net LP v. Flagstar Bancorp*, 653 F.3d 1314, 1322 (Fed. Cir. 2011); *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2004). The Federal Circuit also looks to a patent's title and abstract to inform claim construction. *See, e.g.*, *Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 933 (Fed. Cir. 2019) (title); *UltimatePointer, L.L.C. v. Nintendo Co.*, 816 F.3d 816, 823 (Fed. Cir.

2016) (title); *Hill-Rom Co. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 1341 & n.* (Fed. Cir. 2000) (abstract, collecting cases). Both the '338 Patent's title and abstract explicitly reference treatment, confirming Regeneron's interpretation of the claims. Ex. 1001 at 1 (Title, "Use of a VEGF Antagonist to Treat Angiogenic Disorders"); *id.* (Abstract, "The present invention provides methods for treating angiogenic eye disorders . . . . The methods of the present invention are useful for the treatment of angiogenic eye disorders . . . .").

Enforcing the preamble limitation grounds the claims in this clear utility — treating subjects suffering from angiogenic eye disorders. *See, e.g.*, *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003) (construing the preamble as limiting because without the preamble, "the claimed method reduces to nothing more than a process … whose absence of fathomable utility" is "nothing but an academic exercise."); *E.I. Du Pont de Nemours & Co. v. Monsanto Tech. LLC*, IPR2014-00333, 2014 WL 3507803, at *4-5 (July 11, 2014) (construing the preamble as limiting because the POSA "would not understand the utility of the process" "without construing the preamble language of the claim as limiting"). Thus, the preamble makes clear that the recited dosing regimen must ***treat*** a patient with an angiogenic eye disorder.

Also, the preamble of claims 1 and 14 (which recites "a patient" and "an angiogenic eye disorder") provides an antecedent basis for "the patient" who is treated and for the "angiogenic eye disorders" that are specified in dependent

claims 6, 7, 18, and 20. The method comprises "sequentially administering ***to the patient***" doses of VEGF antagonist in order to treat an angiogenic eye disorder. Ex. 1001, claims 1, 14 (emphasis added). This "sequentially administering" step depends upon the preamble. Without the preamble, it would be unclear ***who*** is receiving sequentially administered doses, *i.e.*, being treated for an angiogenic eye disorder. The MPEP and case law confirm that the use of the indefinite article "a" in the preamble is a signal that it serves as the antecedent basis for the reference to the same object in the body when preceded by the definite article "the." MPEP § 2173.05(e); *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (Fed. Cir. 2008).

Likewise, claims 6, 7, 18, and 20 that recite the particular "angiogenic eye disorder[s]" to be treated rely on the preamble for their antecedent basis. *See id.* at claims 6, 7, 18, and 20. Because the preamble provides an antecedent basis on which other claim limitations rely, it is a positive limitation of the claims. *See, e.g.*, *Sanofi Mature IP v. Mylan Lab'ys Ltd.*, 757 F. App'x 988, 993 (Fed. Cir. 2019) (finding the preamble — "a method of increasing survival" — to be limiting because it provides an antecedent basis for which a later limitation — "a patient in need thereof" — relied); *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001) (finding preamble limiting because otherwise "the phrase 'to a patient in need of such treatment' would not have a proper antecedent basis"); *Gilead Scis, Inc. v. United States*, IPR2019-01455, Paper 16 at 24 (Feb. 5, 2020) (finding

preamble provides information about the body of the claim because "an immunodeficiency retrovirus" provides an antecedent basis for language in the claim body — "the immunodeficiency retrovirus"). Thus, contrary to Petitioner's bald assertion (Pet., 20), the terms "patient" and "angiogenic eye disorder" find antecedent basis in the preamble.

**b. The Preamble Reflects the Efficacy Required by the Body of the Claim**

The preamble requires that the recited method steps produce an effective method of treatment. As discussed above, this construction is supported by the intrinsic record. It is also supported by the body of the claim itself. Claims 1 and 14 require the sequential administration of an initial dose, secondary doses, and one or more tertiary doses. As discussed below, "tertiary dose(s)" require maintaining the efficacy gain of the initial and secondary doses. Thus, the method steps of the body of the claim that require administering an initial dose and one or more secondary doses must result in efficacy, which is maintained with the "tertiary dose(s)." As of January 2011, the POSA would have understood the recited "method of treating" to require efficacy based on the plain language of the claim read as a whole and based on the intrinsic record of the '338 Patent.

Petitioner argues that "the patent does not provide a definition or any metric for what constitutes 'treating' an angiogenic eye disorder" and thus "a [POSA] would apply the term's plain and ordinary meaning: administering a therapeutic to a patient, without a specific degree of efficacy required." Pet., 21. But the

preamble must be construed consistently with the efficacy demanded of the claim as a whole.[8] *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1306 (Fed. Cir. 1999) ("[I]t is essential that the court" "construe the preamble and the remainder of the claim … as one unified and internally consistent recitation of the claimed invention" where the preamble uses language that is repeated in the body of the claim, and is therefore "intimately meshed with the ensuing language in the claim"); *see also Gilead Scis.*, IPR2019-01455, Paper 16 at 24 (finding that the preamble provides "sufficient context" for terms in the body of the claim). As discussed below, the term "tertiary dose(s)" in the body of the claims connotes a specific level of efficacy, and the "method of treating" limitation conforms to this required efficacy and identifies the purpose thereof — for the treatment of an angiogenic eye disorder in a patient.

Finally, Petitioner argues that the preamble is non-limiting (Pet., 17-20) but relies on cases that are factually distinguishable where the claim as a whole, not just the preamble, was found to have no efficacy limitation.

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[8] Contrary to Petitioner's suggestion, (Pet., 20), there is no general rule that efficacy language in a claim is non-limiting. *See, e.g.*, *Gilead Scis,*, IPR2019-01455, Paper 16 at 26 ("Whether such language should be given patentable weight turns on facts unique to each patent.").

### c. The "Tertiary Dose" Must Maintain the Efficacy Gain Achieved After the Initial and Secondary Doses

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 and a straightforward application of Federal Circuit precedent.

Under *Phillips*, claim terms are afforded "their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). But where a term has "no previous meaning to those of ordinary skill in the prior art," one looks "[elsewhere] in the patent." *Irdeto Access, Inc. v. Echostar Satellite Corp.*, 383 F.3d 1295, 1300 (Fed. Cir. 2004).

Both 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.*, 383 F.3d at 1300; *MyMail, Ltd. v. Am. Online, Inc.*, 476 F.3d 1372, 1376 (Fed. Cir. 2007). The parties also agree that "tertiary dose(s)" occur after secondary doses. Ex. 1001, 3:31-38. Stating that the "tertiary dose" comes after the secondary dose, however, does not provide a complete definition of "tertiary dose." Accordingly, the Board must look to the specification as a whole to construe "tertiary dose." *Id.*; *see, e.g., Abraxis*

*Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1376-77 (Fed. Cir. 2006) (construing claim term in light of "the entire specification" not just on a passage purporting to define the term).

The '338 Patent's "entire specification" and prosecution history confirm Regeneron's construction. At the time of filing, therapies for the treatment of angiogenic eye disorders using VEGF antagonists existed in the art. Ex. 1001, 1:49-52. Nonetheless, the '338 Patent recognized that there remained a need for less frequent dosing regimens that could maintain a high degree of efficacy. *Id.* at 1: 55-59. The '338 Patent successfully addressed this long-felt need:

> 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.

*Id.* at 2:3-10 (emphases added).[9]

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[9] Petitioner argues that Regeneron is "reading-in limitations" from the '338 specification, particularly the passage at column 2 that describes "bi-monthly dosing." Pet., 14. Not so. This is not a case where a party has proposed a construction that is consistent only with a single embodiment described in the specification. Rather, the entire specification, and indeed the essence of the

The '338 Patent discloses that a key benefit of the claimed dosing regimens is that for "most of the course of treatment (*i.e.*, the ***tertiary doses***)," *id.* at 2:15-22 (emphasis added), pFFatients may be treated less frequently as compared to therapies that existed in the art. The disclosed dosing regimens were a significant advance over existing therapies because they enabled less frequent dosing while maintaining a high degree of therapeutic efficacy.

During prosecution, Regeneron relied on the unexpected results of the claimed invention to overcome a double patenting rejection because the claimed invention resulted in surprising efficacy despite less frequent dosing than the standard of care (*i.e.*, monthly dosing). Ex. 1017, 288-291, 315. Regeneron's argument during prosecution that less frequent, tertiary dosing "once every 8 weeks" was surprisingly efficacious ultimately resulted in the issuance of the Challenged Claims. Accordingly, the prosecution history confirms that "tertiary dose" connotes a specific level of efficacy.[10]

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invention, teaches that less frequent maintenance doses can be highly effective for the treatment of angiogenic eye disorders.

[10] 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." Pet., 18. But *Purdue* relates to prosecution history estoppel, which is not at issue here.

Petitioner argues that the specification provides an explicit definition for "tertiary dose" that preempts further construction. Pet., 13-14. This is wrong for many reasons.

***First***, the specification does not formally define "tertiary doses," it merely states that "tertiary doses" occur after secondary doses. Ex. 1001, 3:31-38. 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. For example, in *Medicines Company v. Mylan, Inc.*, 853 F.3d 1296, 1306 (Fed. Cir. 2017), the Patent Owner had used an unmistakable format to define certain terms, such as "batches," "pharmaceutical batches" and "drug product." *See id* at 1300. ("'Batches' or 'pharmaceutical batches' as defined herein may include . . . ."). Accordingly, the Federal Circuit held that a different statement, taken directly from the specification, was not definitional, because "it does not accord with the linguistic formula used by the patentee to signal the

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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 preamble term was not discussed during prosecution. But here, "tertiary dose" is in the body of the claim, not the preamble, and regardless, Regeneron's discussion of unexpected results during prosecution was unequivocally related to the "tertiary dose" limitation.

designation of other defined terms – including 'batches.'" *Id.* at 1306.

Here, Regeneron has used a specific "linguistic format" to define terms. *See, e.g.*, Ex. 1001, 3:18-21 ("***As used herein***, the term 'about,' when used in reference to a particular recited numerical value, ***means*** . . . .") (emphases added); *id.* at 3:32-36 ("***As used herein***, 'sequentially administering' ***means*** that each dose of VEGF antagonist is administered to the patient at a different point in time . . . .") (emphases added); *id.* at 4:50-52 ("***As used herein***, the expression 'VEGF antagonist' ***means*** . . . .") (emphases added); *id.* at 5:23-26 ("The expression 'angiogenic eye disorder,' ***as used herein, means*** any disease of the eye . . . .") (emphases added).

Regeneron did not use this linguistic format to describe a "tertiary dose" as occurring after the secondary dose. *See, e.g.*, Ex. 1001, 3:42-44 ("The terms 'initial dose,' 'secondary doses,' and 'tertiary doses,' refer to the temporal sequence of administration of the VEGF antagonist."). Accordingly, the specification does not provide an express definition of "tertiary dose."

***Second***, Petitioner reads this particular passage from the '338 Patent in a vacuum. While Regeneron agrees that the "tertiary dose" is third in sequence, knowing the temporal sequence of administration does not say anything else about the dose. Claim construction, however, requires "consider[ation] [of] the specification as a whole." *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1347 (Fed. Cir. 2020) (reversing claim construction based solely on one statement in the

specification). Considering the entire specification as a whole, it is clear that the 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."

***Third***, Petitioner's argument that Regeneron's proposed construction of "tertiary dose" is "in conflict with the plain language of the '338 claims" (Pet., 14 n.4.) is tautological and presupposes that the claim has been construed to eliminate the efficacy limitations of the claim.

***Fourth***, Petitioner also argues that there is no efficacy requirement recited by the Challenged Claims and cites several distinguishable cases in support. For example, Petitioner relies heavily on *Bristol*, but ignores a critical difference between the Challenged Claims and the claims therein. *See Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). The claimed method steps in *Bristol*, unlike here, "are performed in the same way regardless of whether or not the patient experiences a reduction in the hematologic toxicity" because the *Bristol* claims expressly specify each of the manipulative steps, including the timing and amount of administration, so any functional limitation was found to be superfluous. *Id.* at 1375.[11]

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[11] Bristol attempted to capitalize on this arguing "that the claims of each patent would be infringed without a showing of an objective response in every patient."

In contrast, here, the Challenged Claims do not expressly specify both the dosage amount and the exact frequency of the dosing. Therefore, unlike the claims in *Bristol*, the efficacy limitations of the claim serve to limit and specify the manipulative steps of the claim. *See Gilead Scis.*, IPR2019-01455, Paper 16 at 25 (construing claims to require an efficacy limitation and distinguishing *Bristol* because the claims in *Bristol* "expressly included specific dosage information as material claim elements" whereas the claims-at-issue did not).

Petitioner's other method of treatment cases are likewise distinguishable because they too involve claims that specify the exact dose and frequency, and efficacy would not change the manipulative steps. *See In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1022-23 (Fed. Cir. 2018) (efficacy not required because it "does not change the express dosing amount or method already disclosed in the claims"); *Mylan Lab'ys Ltd. v. Aventis Pharma S.A.*, No. IPR2016-00712, Paper 112 (P.T.A.B. Sept. 22, 2016) (specifying a single dose with a precise frequency).

***Fifth***, Petitioner argues that under Regeneron's construction, the '338 Patent, and related U.S. Patent No. 10,828,345 ("the '345 Patent"), whose tertiary doses are administered at least 12 weeks after the preceding dose, would "require a different construction." Pet., 14 n.4. Not so. While the frequency of the

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*Id.* at 1375. The court explained "Bristol cannot have an expression be limiting in this context and non-limiting in another." *Id.*

"tertiary dose" differs between the '338 claims ($\geq$ 8 weeks apart) and the '345 claims ($\geq$ 12 weeks apart) based on the plain language of the respective claims, this difference is not relevant to Regeneron's proposed construction of "tertiary dose." Regeneron's proposed construction of "tertiary dose" does not require a particular dosing frequency; rather, it requires that the tertiary dose must maintain a certain therapeutic effect.

***Sixth***, Petitioner argues that Regeneron's expected construction "injects ambiguity and indefiniteness where there is none" because the terms "maintain," "therapeutic effect," and "throughout the course of treatment" lack both definition and plain and ordinary meaning. Pet., 15. As an initial matter, Regeneron is not proposing a construction containing the phrase "throughout the course of treatment."[12] And, in any event, Regeneron's construction is clear: the patient continues to maintain the improvement he or she achieved following the initial and secondary doses. Ex. 2001, ¶48. Petitioner fails to explain what about Regeneron's construction is ambiguous.

***Finally***, Petitioner argues that the '338 specification only requires that

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[12] Regeneron proposes slightly different language in its proffered construction of "tertiary dose" than it did in PGR2021-00035 to clarify that the therapeutic effect to which the invention is directed is "maintain[ing] the efficacy gain achieved after the initial and secondary doses."

"efficacy" be a "loss of fifteen or fewer letters in the Early Treatment Diabetic Retinopathy Study ("ETDRS") visual acuity chart within 104 weeks of treatment initiation" based on the specification. Pet. 21; Ex. 1002, ¶43. But the POSA reading the claims in view of the specification and prosecution history would understand that this minimal level of efficacy is not sufficient for the methods of treating claimed in the '338 Patent. For example, if a patient achieved a gain in letters after the initial and secondary doses, then declined after the tertiary dose(s) began, but still exhibited a loss of fewer than 15 letters during the tertiary dosing, the POSA would not consider that to be an effective method of treatment in the context of the '338 Patent. Ex. 2001, ¶48.

Thus, the preamble of claims 1 and 14 is a positive limitation that requires treatment of an angiogenic eye disorder and provides context for the efficacy limitation required by the term "tertiary dose." And the term "tertiary dose" should be construed to mean "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses."

### 2. Petitioner's References Fail To Disclose A "Method Of Treating" Or A "Tertiary Dose"

As noted above, none of Petitioner's cited references expressly discloses an effective method of treatment or a "tertiary dose" that maintains the efficacy gain achieved after the initial and secondary doses. Moreover, Petitioner does not even attempt to show that the administration of "VEGF Trap-Eye," at the disclosed

dosage and dosing intervals as described by the allegedly anticipatory references[13] necessarily results in an effective method of treatment or a "tertiary dose." Because Petitioner fails to show the efficacy limitations were necessarily present in its cited references, institution of the Petition should be denied. *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (inherency "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" to establish inherency.). Moreover, insofar as the Board may not craft new grounds of unpatentability not advanced by the petitioner, it would be inappropriate even to consider such a hypothetical inherency argument. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 935 F.3d 1319, 1326 (Fed. Cir. 2019), cert. denied, 141 S. Ct. 236 (2020).

Indeed, it is known that administration of aflibercept using the claimed dosing regimen will not result in an effective method for treating/tertiary dose for some patients. A retrospective analysis of VIEW (hereinafter "Jaffe") showed 8-week dosing was significantly less effective than monthly dosing in approximately 20% of patients from the VIEW trials. Ex. 2018, 1861 ("[W]hen early persistent fluid was present after the initial 3 injections (a finding present in approximately 20% of eyes initially treated with IAI and in 30% of eyes with Rq4), there may be

[13] Dixon, Adis, Regeneron (8-May-2008), NCT-795 and NCT-377.

a benefit to monthly IAI compared with the other regimens[.]"). Consequently, in 2016, EYLEA®'s label was amended to specify that "***[s]ome*** patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months)." Ex. 2019, 1; *see also id.* ("[A]dditional efficacy was not demonstrated in ***most*** patients when EYLEA was dosed every 4 weeks compared to every 8 weeks.") (emphases added).

Thus, the claimed dosing regimen may not be efficacious in some patients, and consequently, the required efficacy is not inherent in the dosing regimen. *See Gilead Scis.*, IPR2019-01455, Paper 16, 41 ("We are, however, unpersuaded that inherency has been shown on this record. … [B]ased on the evidence here, it is possible (even if 'unlikely') for an individual to receive combination therapy of FTC and DTF (or Truvada) and not be protected from infection.").

Additionally, even if Petitioner had established that "VEGF Trap-Eye" necessarily had the required amino acid and nucleic acid sequence (for the reasons in Section IV.A, it has not), Petitioner's inherency argument also fails to account for other variables that could impact the required efficacy of the claimed dosing regimen. "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must ***necessarily*** include the unstated limitation, [or the reference] cannot inherently anticipate the claims." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed.Cir.2002) (emphasis in original). Neither Petitioner nor its expert account for potential variables in, *inter*

*alia*, the preparation of the VEGF antagonist, its final formulation for administration, or the underlying exclusion criteria for patients to be treated, none of which are specified in Petitioner's cited art. Indeed, the cited references emphasize that special purification and formulation of EYLEA® was necessary for intravitreal administration. *See, e.g.*, Ex. 1006, 1575; Ex. 1005, 2142. What is needed to achieve the required efficacy is absent from any of Petitioner's allegedly anticipating references, and Petitioner makes no effort to show that the disclosed prospective dosing regimen of "VEGF Trap-Eye" necessarily results in a "method of treating" or a "tertiary dose," which require efficacy.

Consequently, Petitioner has not satisfied its burden to show anticipation of a "method of treating" or a "tertiary dose."

### D. Ground 6: Petitioner Fails to Make a Threshold Showing 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) (Ground 6).[14] Petitioner argues that the Challenged Claims would have been obvious in view of Dixon's disclosure of Regeneron's Phase 2, CLEAR-IT 2 clinical trial data — a trial that

[14] Because Petitioner has not sufficiently disclosed its alternative obviousness theories (*see* Section II.B, *supra*), Regeneron addresses Petitioner's failures in Ground 6 as it relates to Dixon only.

tested a different dosing regimen than that claimed in the '338 Patent. Petitioner's Ground 6 argument should be rejected because (1) Petitioner fails to show a reasonable expectation of success of the claimed dosing regimen based on the CLEAR-IT 2 clinical trial results; (2) Petitioner's argument for no objective considerations is premised on a faulty claim construction and is factually flawed; and (3) objective indicia of non-obviousness further support the patentability of the Challenged Claims.

### 1. Petitioner Fails to Show that the POSA Would Have Had a Reasonable Expectation of Success

Petitioner argues that the POSA would have had a reasonable expectation of success for Regeneron's claimed Q8 dosing regimen in view of the positive Phase 2 [CLEAR-IT 2] data for VEGF Trap-Eye disclosed in Dixon. Pet., 64-65. But Petitioner fails to address significant differences between Regeneron's Phase 2 dosing regimen and the prospective Phase 3 dosing regimen. Petitioner also cherry-picks Regeneron's Phase 2 clinical trial results to suggest incorrectly that success for Regeneron's Phase 3 pivotal trial was expected. Not only is Petitioner's assertion unsupported by the factual record, but the published results of CLEAR-IT 2, the prior failures for extended dosing regimens, and the clinical trial design for VIEW1/2 demonstrate that there was great uncertainty as to whether Regeneron's extended fixed dosing regimen (with $\geq$ 8 weeks maintenance dosing) would work until Regeneron proved that it could.

***First***, Petitioner suggests that the very fact that Regeneron chose to run

Phase 3 trials means that the POSA would have expected the 8-week dosing regimen to be successful.[15] Pet., 64. Likewise, Petitioner's expert, Dr. Albini, states "Regeneron would not have settled on [3 monthly loading dose/every-8-week in the VIEW studies] without having a reasonable expectation that it would be successful." Ex. 1002, ¶368. Thus, Petitioner and its expert impermissibly work backwards from Regeneron's own inventive path, using improper hindsight. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to obviousness; that is hindsight."). The Board should not follow Petitioner's lead and assess the validity of the Challenged Claims using this "illogical and inappropriate process." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996); *see also Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.").

Large-scale Phase 3 clinical trials routinely fail, even when a Phase 2

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[15] Petitioner misleadingly suggests that "Dixon reports, the Phase 2 CLEAR-IT 2 AMD trials were so promising that Phase 3 trials involving > 2000 patients were launched." Pet., 64. Dixon says no such thing. To the contrary, as discussed *infra*, Dixon notes that the Phase 3 VIEW results are required to know whether VEGF Trap-Eye will offer longer duration therapy.

clinical trial shows promise. Indeed, the art is littered with Phase 3 clinical trial failures of VEGF inhibitors for angiogenic eye disorders. Ex. 2020, 1-2; Ex. 2021, 1-2 (lampalizumab Phase 3 clinical trials, enrolling 975 and 906 patients, failed to meet primary endpoints); Ex. 2022, 1-2; Ex. 2023, 1-2 (Conbercept Phase 3 clinical trials, enrolling 1,157 and 1,157 patients, failed to meet primary endpoints); Ex. 2024, 1-2; Ex. 2025, 1-2 (Fovista Phase 2 clinical trials, enrolling 619 and 627 patients, failed to meet primary endpoints).

Thus, the fact that Regeneron initiated a Phase 3 clinical trial is not *prima facie* evidence of a reasonable expectation of success. *See OSI Pharms. LLC v. Apotex Inc.*, 939 F.3d 1375, 1378-79 (Fed. Cir. 2019) (finding that initiation of phase 2 trials does not show reasonable expectation of success). Indeed, both Fovista and Conbercept failed to meet their primary endpoints in Phase 3 studies, despite promising Phase 2 results. Ex. 2024; Ex. 2025; Ex. 2026, 1; Ex. 2022; Ex. 2023; Ex. 2027, 1.

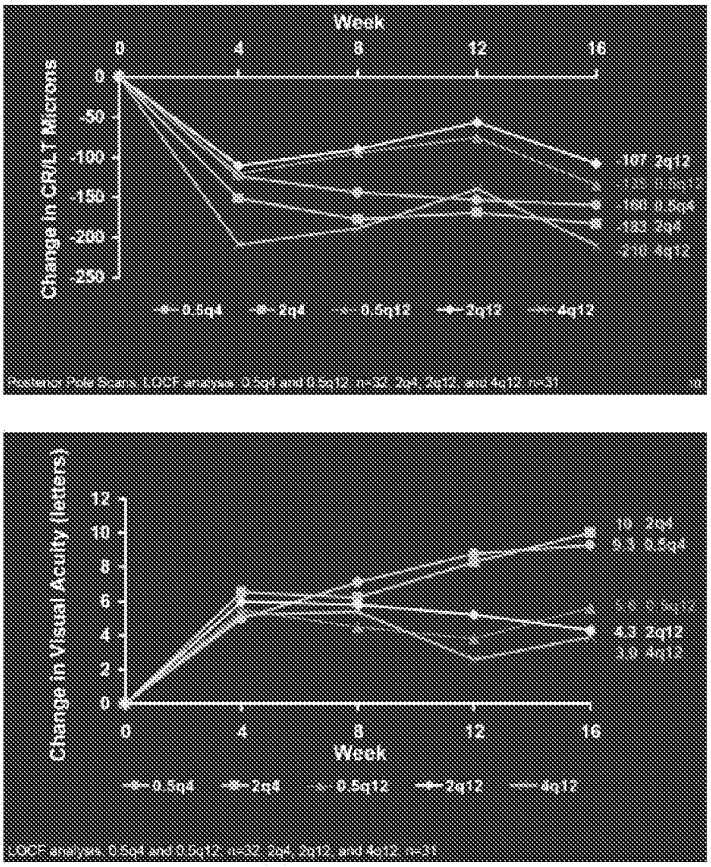
Perhaps most tellingly, the design of the VIEW1/2 trials demonstrates that Regeneron itself was hedging its bets on an extended 8-week dosing regimen. VIEW1/2 tested three treatment arms against a ranibizumab non-inferiority comparator — a 0.5 mg monthly dosing arm, and both a 4-week and 8-week 2 mg dosing arm (following three monthly loading doses). *See* Ex. 1006, 1576. 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 treatment

arms. An additional treatment arm significantly increases the time and expense (by millions of dollars) required to conduct a clinical trial. The added expense and effort would make no sense if Regeneron had a reasonable expectation that its prospective 8-week maintenance dosing arm would be successful.

***Second***, Petitioner argues that Dixon's disclosure of positive Phase 2 results from CLEAR-IT 2 (testing four monthly loading doses followed by PRN dosing) would have provided the POSA with a reasonable expectation of success. Pet., 64-65. To the contrary, the CLEAR-IT 2 trial results called into question the viability of an 8-week dosing regimen for VEGF Trap-Eye.

The CLEAR-IT 2 12-week primary endpoint data indicated that the therapeutic effect of VEGF Trap-Eye began to decrease between the week-4 and week-8 timepoints in the quarterly dosing arms, and the only treatment arms that were successful in sustaining therapeutic efficacy were the monthly treatment dosing arms (*i.e.*, 0.5Q4 and 2Q4). This is shown in the figure below, which was presented at the September 30, 2007, Retina Society Conference in Boston,

Massachusetts. Ex. 2028.




The top panel reports on central retinal/lesion thickness. A decrease in retinal thickness generally corresponds to a drying of the macula and the fluid that is created by the angiogenic process of wet AMD. The bottom panel reports visual acuity. As shown at the 8-week timepoint, there is re-accumulation of fluid by week 8 in the top figure (curves for arms 0.5Q12, 2Q12 and 4Q12 trend upward) in the treatment arms that received a dose at week 0 and a dose at week 12. This increased retinal thickness trend continues through week 12. The POSA

would have understood that fluid reaccumulation between weeks 4 and 8 on CRT would strongly suggest that VEGF Trap-Eye has less durability than 8 weeks. Likewise, in the bottom figure, visual acuity decreased at week 8 in the 0.5Q12 and 2Q12 arms relative to visual acuity at week-4, suggesting that VEGF Trap-Eye's effect was waning sometime between week-4 and week-8. Thus, 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.

***Third***, there was great uncertainty in the art regarding extended dosing based on prior failures, which Petitioner ignores. For example, Heier 2012 explains: "fixed quarterly[9,10] or 'as needed' (*pro re nata* [PRN]) dosing regimens,[11,12] without requiring monthly monitoring visits, were not effective at maintaining vision." Ex. 1018, 2537. Notably, Heier 2012 cites the same clinical trials on which Petitioner attempts to rely — EXCITE (Ex. 2029, 803; Ex. 2030, 3) (resulting in inferior therapeutic outcomes with quarterly as compared to monthly dosing of ranibizumab); HORIZON (Ex. 2029, 803) (resulting in inferior therapeutic outcomes with PRN dosing as compared to monthly dosing of ranibizumab); PIER (Ex. 2031, 680; Ex. 1027, 1425 ) (resulting in inferior therapeutic outcomes with quarterly dosing as opposed to monthly dosing of ranibizumab); and SAILOR (Ex. 2032, 1738) (resulting in inferior therapeutic outcomes with PRN dosing as compared to monthly dosing of ranibizumab) —

but reaches the opposite conclusion, *i.e.*, that these dosing regimens were not effective at maintaining vision. Indeed, Dixon notes that the PIER and PrONTO studies "seem to indicate that quarterly dosing is associated with poorer outcomes, but it may be possible to extend the time between injections if the patient is frequently monitored." Dixon at 1574, 1577.

Finally, nothing in Dixon itself taught that a fixed extended dosing regimen was likely to work. To the contrary, Dixon cautioned against over-interpreting Phase 2 results:

> ***The most effective dosing regimen and monitoring program for anti-VEGF therapy has yet to be firmly established*** but new treatments are aimed at extending and improving on the efficacy of ranibizumab.

Ex. 1006, 1576-77 (citations omitted) (emphasis added). In fact, Dixon notes that the durability of VEGF Trap-Eye and its adoption in clinical practice will only be known after Regeneron's Phase 3 clinical trial results are reported:

> Data from the Phase II study with VEGF Trap-Eye were positive .... ***Its adoption into clinical practice will depend on efficacy at 4 and 8 week intervals.*** If effective at 4 week intervals only, VEGF Trap-Eye will be adopted into clinical practice if it offers a competitive price advantage over ranibizumab. ***If effective at 8 week intervals, VEGF Trap-Eye offers the opportunity to significantly reduce treatment burden on patients and physicians, which would probably find wide acceptance.***

Ex. 1006, 1577 (citations omitted) (emphases added).

### 2. Petitioner's Argument Against Objective Evidence Should Be Rejected

The Federal Circuit has "repeatedly held that . . . objective evidence of secondary considerations . . . must be considered before determining whether the claimed invention would have been obvious." *Apple, Inc. v. ITC*, 725 F.3d 1356, 1365 (Fed. Cir. 2013). Such objective indicia include long-felt but unsolved need, unexpected results, and commercial success. *Id.* at 1375.

***First***, Petitioner's arguments against objective evidence are premised on a faulty claim construction that ignores the efficacy limitations of the Challenged Claims. Pet., 66. Petitioner argues that, because the claims do not require efficacy, the unexpected efficacy results of the claimed dosing regimen are irrelevant. Petitioner cites *Ormco* and *Kao* for the proposition that "if the [objective indicia] is due to an unclaimed feature of the device, the [objective indicia] is irrelevant." *Id.* But the objective indicia supporting nonobviousness of the Challenged Claims is directly tied to the claimed extended dosing regimens.

***Second***, Petitioner argues that Regeneron's showing of unexpected results during prosecution was flawed because it allegedly omitted "highly pertinent" information from the Examiner. This is incorrect and Petitioner's argument lacks merit.

Petitioner asserts Regeneron failed to disclose pre-January 2011 disclosures of the prospective VIEW1/2 dosing regimen to the Examiner. Pet., 67. But, as

detailed in Section III.B above, this is not so. For example, the 9/28/08 Press Release, which sets forth an identical disclosure to the disclosures on which Petitioner now relies for its anticipation arguments, was submitted to and considered by the Examiner.

Petitioner also contends that Regeneron mischaracterized "the standard of care at the time as monthly dosing, which ignored the actual practice of ophthalmologists at the time, who had begun using PRN or treat-and-extend dosing after a series of monthly loading doses." *Id.* But there was no satisfactory extended dosing regimen available at the time of the invention.

Before Regeneron's invention, there were two approved anti-VEGF therapies in use in clinical practice — Lucentis® and Avastin®.[16] Avastin, approved only for oncology indications, was used off-label and the FDA-approved, recommended label dosing for Lucentis was monthly intravitreal injections. Ex. 2003 ("recommended to be administered by intravitreal injection once a month (approximately 28 days)."). Petitioner points to various ranibizumab clinical trials to suggest that PRN or "less frequent dosing" was the standard of care, but those trials showed that PRN and quarterly dosing were not as effective and did not change the standard of care. Even today, the

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[16] Macugen, an anti-VEGF aptamer, was also approved for the treatment of AMD, but its use was largely minimal once Lucentis was approved.

recommended administration of Lucentis remains monthly injections. Ex. 2033.

Next, Petitioner argues that "there is nothing unexpected about the every-eight-week results in light of the Phase 2 results obtained by Regeneron—results that were omitted from their arguments to the Examiner." Pet., 67. This argument belies the facts. Regeneron's Phase 2 results were submitted to and considered by the Examiner, including in the 9/28/08 Press Release. Ex. 2007. As explained in Section IV.D.1, *supra*, Regeneron's Phase 2 clinical trial data, which tested a completely different dosing regimen, did not prophesy the results of the claimed dosing regimen. It was not until the VIEW1/2 results were published that it was known that an 8-week dosing regimen could be successful, and, surprisingly, that it could be non-inferior to monthly dosing with ranibizumab.

Petitioner also argues "Regeneron's claims of 'an infinite number of different treatment protocols' to choose from ignored the practical realities facing physicians at the time." Pet., 68. While it is unclear how this statement is relevant to Regeneron's showing of unexpected results, Petitioner's statement is unfounded. Regeneron made this statement in response to an obviousness-type

double patenting rejection based on the Weigand Patents,[17, 18] which even the Examiner recognized did not "disclose the dosing schedules set forth in the instant claims." Ex. 1017. at 266.

Additionally, Petitioner's unsupported attorney argument that "[monthly] dosing would have been avoided if possible," "anything more frequent than monthly dosing would not have been considered," and "a new entrant to the anti-VEGF market naturally would have considered bi-monthly or quarterly dosing" (Pet., 68) is contradicted by the FDA-approved label for Lucentis® and the fact

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[17] U.S. Patent No. 7,303,746 ("the '746 Patent"), U.S. Patent No. 7,303,747 ("the '747 Patent"), U.S. Patent No. 7,306,799 ("the '799 Patent"), and U.S. Patent No. 7,521,049 ("the '049 Patent") (collectively, "the Wiegand patents").

[18] Petitioner improperly refers to the Wiegand patents as "Monthly-Dosing Patents." Pet., 9 n.3. There is nothing to suggest that the Wiegand patents are directed to "monthly dosing regimens." Neither the '746 Patent nor the '049 Patent claim any particular dosing regimen or dosing interval. Ex. 2034, 69:50-70:60; Ex. 2035, 39:38-42:5. And the '747 Patent and '799 Patent recite a variety of dosing intervals, *e.g.*, "at least two weeks apart," "at least 4 weeks apart," "at least 3 months apart," or "at least 6 months apart." Ex. 2036, 39:66-42:3; Ex. 2037, 39:40-40:44.

that Macugen was approved for 6-week dosing. Ex. 2038.

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: "[b]y 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." Pet., 69. Petitioner disregards that it was not until the inventions of the '338 Patent, ***after*** the VIEW1/2 study results were obtained that anyone, including Regeneron, understood the that the remarkable advantage of fixed 8-week dosing could be realized.

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 widely used for the treatment of wAMD and other angiogenic eye disorders. Nonetheless, Regeneron's U.S. sales of EYLEA® have grown significantly since launch. Ex. 2039, 1; Ex. 2040, 4 . Petitioner's assertion that the '338 Patent's claimed dosing regimens were obvious before January 2011 is contradicted by the extraordinary commercial success that EYLEA® has enjoyed since launch.

In the unlikely event it is required, Regeneron can and will present additional compelling evidence of objective indicia, including at least (1) commercial success of EYLEA®; (2) the claimed treatment produced unexpected results; (3) others have tried and failed to develop a treatment capable of extended,

fixed dosing; and (4) long-felt but unmet need for an extended dosing regimen.

## V. CONCLUSION

For the foregoing reasons, the Board should deny institution of MPI's petition for IPR of all Challenged Claims of the '338 Patent.

Dated: August 16, 2021

Respectfully Submitted,

*/s/ Deborah E. Fishman*

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**Counsel for Patent Owner,**
**Regeneron Pharmaceuticals, Inc.**

## CERTIFICATE OF COMPLIANCE

The undersigned certifies that this preliminary response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This preliminary response (including figure labels and annotations) contains 13,928 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 preliminary 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 preliminary response has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14-point font.

*/s/ Deborah E. Fishman*

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**Counsel for Patent Owner,**
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## CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq*. and 42.105(b), the undersigned Certifies that on April 14, 2021, a true and entire copy of this **PRELIMINARY RESPONSE OF PATENT OWNER REGENERON PHARMACEUTICALS, INC.**, and all supporting exhibits, were served via e-mail to the Petitioner at the following email addresses:

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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*Inter Partes* Review No.: IPR2021-00881

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

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

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**EXPERT DECLARATION OF DR. THOMAS A. ALBINI IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,254,338 B2**

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1. My name is Dr. Thomas A. Albini. I have been retained by counsel for Mylan Pharmaceuticals Inc. ("Mylan" or "Petitioner") to provide my opinion regarding U.S. Patent No. 9,254,338 (Ex.1001, the "'338 patent"), which I understand is assigned to Regeneron Pharmaceuticals, Inc. ("Regeneron"). I understand that Petitioner intends to petition for *inter partes* review of the '338 patent, and will request that the United States Patent and Trademark Office cancel certain claims of the '338 patent as unpatentable. My opinions in this expert declaration support Petitioner's request for *inter partes* review of the '338 patent and the cancellation of claims 1, 3-11, 13-14, 16-24, and 26 (the "challenged claims").

## I. QUALIFICATIONS AND BACKGROUND.

### A. Education and Experience.

2. I received a Bachelor of Arts degree, *Magna Cum Laude*, from Princeton University in 1994. I obtained my M.D. from Johns Hopkins University School of Medicine in 1999. I completed an internal medicine internship at Jackson Memorial Hospital in Miami, Florida, and an ophthalmology residency at the Doheny Eye Institute of the University of Southern California.

3. After my residency, I completed a uveitis and ocular pathology clinical and research fellowship at the Doheny Eye Institute followed by a vitreoretinal surgery fellowship at the Cullen Eye Institute of the Baylor College of Medicine.

4. I was an instructor in ocular inflammation, uveitis, and ophthalmic pathology at the Doheny Eye institute from 2003-2004. I joined the faculty at the Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine as an Assistant Professor of Clinical Ophthalmology in 2006. I held the position of Associate Professor of Clinical Ophthalmology at the Bascom Palmer Eye Institute from 2012 to June 2018. Since July 2016, I have served as co-director of the vitreoretinal surgery fellowship. Since June 2018, I have been a Professor of Clinical Ophthalmology. In my current and prior positions, I have been involved in the teaching and training of medical students, fellows, and residents in the area of ophthalmological surgical techniques, specifically, injection protocols for the administration of therapeutics for the treatment of age-related macular degeneration (AMD) and other vitreoretinal eye disorders. Further, in 2006, I began my current roles as a staff ophthalmologist at both the Anne Bates Leach Eye Hospital of the Bascom Palmer Eye Institute as well as the Jackson Memorial Hospital.

5. I was awarded the American Academy of Ophthalmology Achievement Award in 2011 and Senior Achievement Award in 2019. In 2012, I received the Service Award from the American Society of Retina Specialists for outstanding service to the Society's scientific and educational programs. I also received the Senior Honor Award from the American Society of Retina Specialists in 2012.

6. I have served as an editor, co-editor, or on the editorial board of several publications, including Retina Today, the website for the American Society of Retina Specialists, New Retina MD, and the Journal of VitreoRetinal Diseases.

7. My clinical practice is focused on the diagnosis and treatment of patients suffering from various macular diseases, such as macular degeneration, diabetic retinopathy and related disorders, as well as uveitis. I have experience with surgical interventions as well as the prescription and administration of various intravitreally-administered anti-angiogenesis agents.

8. I was and currently am a member in several Professional and Academic Societies, including American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology, American Society of Retina Specialists, Miami Ophthalmological Society, Vitrectomy Buckle Society, American Uveitis Society, The Macula Society, Pan American Association of Ophthalmology, and The Retina Society, among others.

9. I have authored or co-authored over two hundred and fifty (250) publications, including book chapters, peer-reviewed scientific papers, abstracts, and other published works. Several of these publications pertain to AMD, retinal detachment, retinal and choroidal diseases, or diabetic macular edema (DME), among other disorders of the eye.

10. In all, I have over fifteen (15) years of hands-on clinical and research experience specializing in treating vitreoretinal disorders and the prescription, and intravitreal administration, of VEGF antagonists. I have included a copy of my *curriculum vitae* in support of my opinions. (Ex.1038, Albini CV).

**B. Bases for Opinions and Materials Considered.**

11. In addition to my education, knowledge of the relevant published art, training, and experience, in forming the opinions I provide in this declaration, I have also considered the exhibits cited herein.

**C. Scope of Work.**

12. I have been retained by Petitioner as an expert in this matter to provide my various opinions regarding the '338 patent. I receive $500 per hour for my services. No part of my compensation is dependent upon my opinions given or the outcome of this case. I do not have any current or past affiliation with Regeneron, or any of the named inventors on the '338 patent.

## II. LEGAL STANDARDS.

13. For my opinions in this declaration, I understand that it requires applying various legal principles. As I am not an attorney, I have been informed about various legal principles that govern my analysis. I have used my understanding of those principles in forming my opinions. I summarize my understanding of those legal principles as follows:

14. **Burden of Proof.** I understand that Petitioner bears the burden of proving unpatentability in this proceeding by a preponderance of the evidence. I am informed that this preponderance of the evidence standard means that Petitioner must show that unpatentability is more probable than not.

15. **Claim Construction.** I have also been told that when I review and consider the claims, the claim term(s) should be analyzed under their ordinary and customary meaning as understood from the perspective of one of ordinary skill in the art, taking into account the claim language itself, specification, and prosecution history pertaining to the patent, as well as relevant extrinsic evidence. I have applied this standard in formulating my opinions, and set forth my understanding of the scope of particular claim terms discussed below.

16. **Anticipation.** I have been asked to consider the question of anticipation, namely, whether the claims cover something that is new, or novel. I am told that the concept of anticipation requires that each and every element of a challenged claim is present in or otherwise taught by a single reference. I also understand that an anticipatory reference does not need to explicitly describe each element because anticipation can occur when a claimed limitation is necessarily inherent or otherwise implicit in the relevant reference.

17. **Obviousness.** I have been asked to consider the question of obviousness/non-obviousness. Again, I am told that this analysis must be from the

perspective of the person of ordinary skill in the art, and whether such person would consider any differences between the prior art and what is claimed to have been obvious. To make this assessment, I have been informed that the concept of patent obviousness involves four factual inquiries:

- the scope and content of the prior art;
- the differences between the claimed invention and the prior art;
- the level of ordinary skill in the art; and
- so-called secondary considerations of non-obviousness.

18. I have further been instructed that one cannot use the challenged patent itself (here, the '338 patent) as a guide from which to select prior art elements, or otherwise engage in hindsight. Rather, the better approach is to consider what the person of ordinary skill in the art knew, and what the art taught; suggested; or motivated the person of ordinary skill in the art to further pursue; and to differentiate between steps that were routinely done (such as in response to known problems, steps, or obstacles), and those which, for example, may have represented a different way of solving existing or known problems.

19. I am also informed that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected

success, it is likely not the product of innovation but of ordinary skill and common sense. In addition, when a patent simply arranges old elements with each performing its known function and yields no more than what one would expect from such an arrangement, the combination is obvious.

20. I understand that before reaching any final conclusion on obviousness, the obviousness analysis requires consideration of objective indicia of non-obviousness, if offered. These must be considered to ensure that, for example, there were not some unanticipated problems, obstacles, or hurdles that may seem easy to overcome in hindsight, but which were not readily overcome prior to the relevant invention date of the patents/claims at issue here. I understand that these objective indicia are also known as "secondary considerations of non-obviousness," and may include long-felt but unmet need and unexpected results, among others. I also understand, however, that any offered evidence of secondary considerations of non-obviousness must be comparable with the scope of the challenged claims. This means that for any offered evidence of secondary considerations of non-obviousness to be given substantial weight, I understand the proponent of that evidence must establish a "nexus" or a sufficient connection or tie between that evidence and the merits of the claimed invention, which I understand specifically incorporates any novel element(s) of the claimed invention. If the secondary considerations evidence offered actually results from something other than the merits of the claim, then I

understand that there is no nexus or tie to the claimed invention. I also understand it is the patentee that has the burden of proving that a nexus exists.

21. With respect to long-felt need, I understand that the evidence must show that a particular problem existed for a long period of time. More specifically, I understand that for a "need" to be long-felt and unmet, (i) the need must be persistent and recognized by those of ordinary skill in the art; (ii) the need must not be satisfied by another before the alleged invention; and (iii) the claimed invention itself must satisfy the alleged need. I also understand that long-felt need is analyzed as of the date that the problem is identified. Furthermore, I understand that long-felt need should be based upon alleged inadequacies in the technical knowledge of those skilled in the art, not due to business-driven market forces.

22. I further understand that, absent a showing of a long-felt, unmet need, the mere passage of time without the claimed invention is not evidence of non-obviousness.

23. With respect to unexpected results, I understand that any results upon which a patentee wishes to rely as an indicator of non-obviousness must be based on a comparison of the purported inventions with the closest prior art.

24. However, I understand that secondary considerations will not overcome a strong showing of obviousness.

25. **Public Availability.** I have also been asked to consider whether there is a reasonable likelihood that some of the references discussed herein would have been publicly accessible before the priority date of the '338 patent. I have been informed that a reference is "publicly accessible" if the document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it.

## III. PERSON OF ORDINARY SKILL IN THE ART.

26. As I mentioned above, I have been informed by counsel that my analysis is to be conducted from the perspective of a person of ordinary skill in the art at the time of the invention. I also understand that the person of ordinary skill in the art is assumed to know, understand, and be familiar with all of the relevant prior art, and that such person is not an automaton, but rather a person of ordinary creativity.

27. I have also been informed by counsel that in defining a person of ordinary skill in the art, the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field.

28. After considering the above-mentioned factors, it is my opinion that a person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in: (i) developing treatments for angiogenic eye disorders, such as AMD, including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

## IV. SUMMARY OF OPINIONS.

29. It is my opinion that Dixon anticipates the challenged claims of the '338 patent through Dixon's disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW1 and VIEW2 AMD trials (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

30. It is my opinion that Adis anticipates the challenged claims of the '338 patent through Adis' disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW1 and VIEW2 AMD trials (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

31. It is my opinion that Regeneron's May 2008 Press Release ("Regeneron (8-May-2008)") anticipates the challenged claims of the '338 patent through the disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW2 AMD trial (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

32. It is my opinion that Regeneron's publicly accessible clinicaltrials.gov submissions (NCT-795 and NCT-377) also anticipate the challenged claims of the '338 patent through their disclosure of the dosing regimen used by Regeneron in their Phase 3 VIEW1 and VIEW2 AMD trials (3 monthly doses of 2 mg, followed by 2 mg every eight weeks).

33. It is my opinion that the public disclosures of Regeneron's VIEW1/VIEW2 trials make the challenged claims obvious, because they disclose all aspects of the claimed dosing regimen, and because combined with the skilled person's knowledge regarding the VEGF Trap-Eye/aflibercept sequence and structure (as disclosed in the '758 patent and Dix), as well as the motivation in the art to reduce injection frequency, and the positive results observed in the Phase 2 CLEAR-IT clinical trials, persons of ordinary skill in the art would have had a reasonable expectation of success in using the VIEW1/VIEW2 regimens.

34. It is also my opinion that there are no "secondary considerations" that would support the patentability of the claims of the '338 patent. First, it is my understanding that secondary considerations are not relevant in the context of

anticipation and it is my opinion that each of the VIEW1/VIEW2 disclosures mentioned above anticipate the '338 patent claims. Second, in the context of obviousness, it is my opinion that the arguments presented by Regeneron to the U.S. Patent and Trademark Office do not support a finding of surprising or unexpected results, especially given the positive and promising results reported for the Phase 2 trial and public disclosure of the Phase 3 dosing regimen.

## V. THE '338 PATENT (Ex.1001).

35. I have read the '338 patent, which is titled "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders," as well as the issued claims. I am very familiar with the state of the art at the time this patent was first filed, which I have been asked to assume is January 13, 2011.[1] The '338 patent lists George D. Yancopoulos as the sole inventor.

[1] I understand the following from the cover page of the '338 patent: (i) Application No. 13/940,370 ("the '370 application") issued as the '338 patent on or about February 9, 2016; (ii) the '370 application was filed July 12, 2013; (iii) as a "continuation-in-part" of application No. PCT/US2012/020855, which was filed on January 11, 2012; and (iv) the '338 patent lists three "provisional" applications filed, respectively, on (a) January 13, 2011; (b) January 21, 2011; and (c) November 21,

36. I have reviewed the '338 patent claims from the perspective of a person of ordinary skill in the art and applied each claim's ordinary and customary meaning in light of the claims, the specification, and the prosecution history, as well as any relevant extrinsic evidence. I understand that Petitioner is challenging claims 1, 3-11, 13-14, 16-24, and 26.

37. Claims 1 and 14 are the only independent claims and read as follows:

> **1**. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2.

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2011, as "Related U.S. Application Data." (*See* Ex.1001, '338 patent at Cover). I have been asked to assume that the priority date of the '338 patent is January 13, 2011. I have formed no opinion regarding the merit of the '338 patent's claim to that date.

* * *

> **14**. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

(Ex.1001, '338 patent, 23:2-18 (claim 1); *id.*, 24:3-15 (claim 14)).

38. Challenged claims 3-11 and 13 all depend, either directly or indirectly, from claim 1.

39. Challenged claims 16-24 and 26 all depend, either directly or indirectly, from claim 14.

**A. Claim Construction.**

40. In my opinion, a person of ordinary skill in the art would reach at least the following conclusions regarding the claim language:

41. **First**, although the terms "initial dose," "secondary dose," and "tertiary dose" are not typically used in practice, a person of ordinary skill in the art would understand the terms to have the meaning expressly given to them in the '338 patent specification:

> The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses.

(*See* Ex.1001, '338 patent, 3:31-38). The '338 patent further states that "[t]he initial, secondary, and tertiary doses…will generally differ from one another in terms of frequency of administration." (*Id.*, 3:38-41). For example, the '338 patent states that "each secondary dose is administered 2 to 4…weeks after the immediately preceding dose, and each tertiary dose is administered at least 8…weeks after the immediately preceding dose." (*Id.*, 3:46-51). The '338 patent explains that "the immediately preceding dose" means "in a sequence of multiple administrations, the dose of VEGF antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses." (*Id.*, 3:51-56). These are the meanings I have applied to these terms in formulating my opinions.

42. **Second**, to a person of ordinary skill, the reference to administering at "4 weeks" in the claims is synonymous in the art with treating angiogenic eye disorders with *monthly* administration. Likewise, the reference to "administered at least 8 weeks" is synonymous in the art with treating angiogenic eye disorders with

*bi-monthly* (or every-other-month) administration. This is also consistent with my own experience treating angiogenic eye disorders—i.e., I consider "4 weeks" to be synonymous (or interchangeable) with "monthly," and "8 weeks" to be synonymous (or interchangeable) with "bi-monthly," (or every-other-month). (*See id.*, 7:54-56).

43. **Third,** although I have been informed that a claim preamble is presumed not to be a claim limitation, I have been asked for my opinion on the scope of the term "method for treating" should the Board wish to construe the term. In my opinion, without any parameters set forth in the claim or any additional guidance from the claim itself, a person of ordinary skill in the art would apply a plain and customary meaning to the term, which would include administering a therapeutic agent to a patient. I have analyzed the specification and have not seen an alternative definition for the term in the specification. I have seen a reference to "efficacy," and if one were to equate a method for treating with a particular efficacy, the definition in the patent provides that the method demonstrate efficacy within 104 weeks from initiation, and that the patients exhibit a loss of 15 or fewer letters on the ETDRS visual acuity chart. (*Id.*, 7:16-31).

44. **Fourth**, with respect to claims 1 and 14 (and the claims that depend therefrom), a person of ordinary skill in the art would understand the "VEGFR1 component," "VEGFR2 component," and the "multimerization component"—all of which refer to separate amino acid domains of "SEQ ID NO:2" and the

corresponding DNA sequence of "SEQ ID NO:1"—as collectively referring to aflibercept (a/k/a VEGF Trap or VEGF Trap-Eye), for at least the following reasons:

- The amino acid sequence provided in the '338 patent specification for "SEQ ID NO:2" is the identical amino acid sequence Regeneron previously submitted to the U.S. Patent and Trademark Office as referring to aflibercept (a/k/a VEGF Trap or VEGF Trap-Eye).[2] (*Compare id.*, SEQ ID NO:2, *with* Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); *see also, e.g.*, Ex.1024, '758 FH, 12/22/2011 Patent Term Extension Application, 2, 6-7 ("The name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP$_{R1R2}$ . . . [,] a fusion protein consisting of (a) a vascular

[2] In the course of my analysis, I requested that exhibits be created that compare the SEQ ID NO:1 and SEQ ID NO:2 of the '338 patent with sequences disclosed in the prior art references. I have reviewed these exhibits and confirmed that these sequences are the same. (Ex.1093; Ex.1094).

endothelial growth factor (VEGF) receptor component having immunoglobulin-like (Ig) domains consisting of an Ig domain 2 of a first VEGF receptor that is human Fltl and an Ig domain 3 of a second VEGF receptor that is human Flkl; and (b) an Fc portion of human IgG1," and further explaining to the U.S. Patent and Trademark Office that the amino acid sequence of aflibercept is set forth in Figures 24A-24C of the '758 patent));

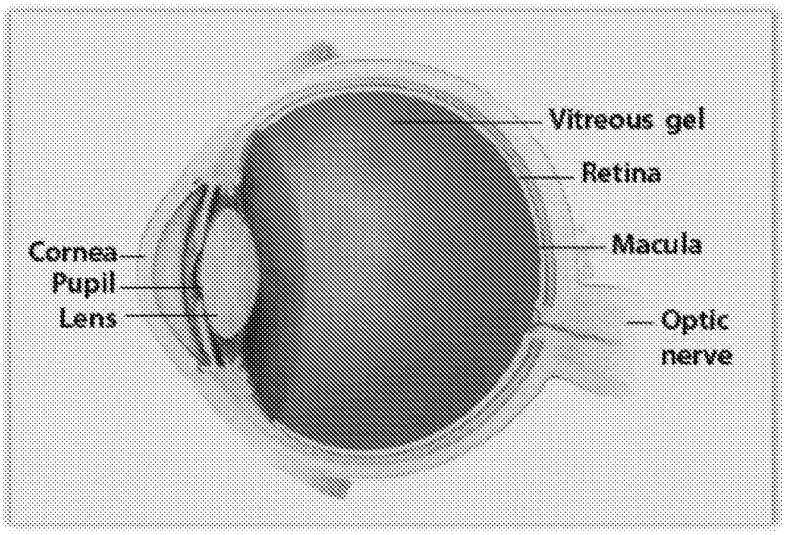
- The '338 patent specification states that "[a]n exemplary VEGF antagonist that can be used in the context of the present invention is a multimeric VEGF-binding protein comprising two or more VEGF receptor-based chimeric molecules referred to herein as 'VEGFR1R2-FcΔC1(a)' or 'aflibercept.'" (Ex.1001, '338 patent, 2:32-37); and
- It was well known in the art that this fusion VEGF antagonist was commonly referred to as "VEGF Trap," and also known as "aflibercept," as well as "VEGF Trap-Eye" when formulated for intraocular delivery. These terms were often used interchangeably by those of ordinary skill in the art. (*See, e.g.*, Ex.1006, Dixon, 1575 ("VEGF Trap-Eye and aflibercept (the oncology product) have the same molecular structure."); Ex.1039, '095 patent, 1:45-54; Ex.1040, WHO Drug Info, 118-19; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept

interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug)).

## VI. BACKGROUND.

### A. Vitreoretinal Disorders.

45. The following Figure illustrates the normal anatomy of the eye:




(Ex.1042, NIH AMD, 2). Vitreoretinal disorders relate to problems involving the retina, macula, and vitreous fluid (or gel). The retina is the light-sensitive tissue lining the back of the eye, which converts light rays into impulses that travel through

the optic nerve to the brain, where they are interpreted as images. The macula is the small area at the center of the retina, which, because of the high concentration of cones in that region, is responsible for high-acuity color vision, which enables one to distinguish among different colors. The vitreous fluid (or gel) is the clear, jelly-like substance that fills the inside of the eye from the lens to the retina, helping the eye maintain its shape.

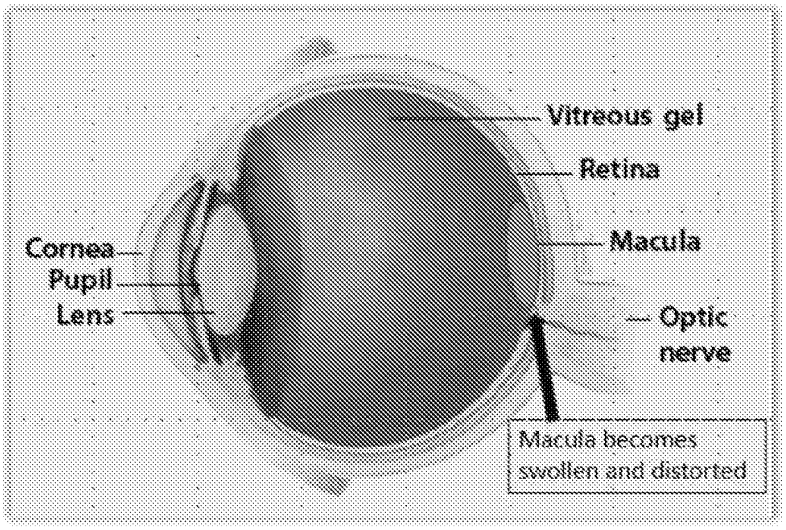
46. Vitreoretinal disorders such as AMD and diabetic retinopathy (DR) are the leading causes of visual impairment in developed countries, and the prevalence of these disorders is expected to rise with the increase in the aged population. (*See* Ex.1006, Dixon, 1573).

**1. Age-related macular degeneration (AMD).**

47. The NIH's National Eye Institute describes AMD as "a common eye condition and a leading cause of vision loss among people age 60 and older. It causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead." (Ex.1042, NIH AMD, 1).

48. AMD can be classified as either "dry" (nonexudative) or "wet" (exudative). (*See, e.g.*, Ex.1036, Regeneron (28-April-2008), 2). In wet AMD, new blood vessels grow beneath the retina and leak blood and/or fluid, causing disruption

and dysfunction of the retina, as I have illustrated in the following modification of Figure 1 from NIH AMD:




(Ex.1042, NIH AMD, 2 (modified to illustrate neovascular (wet) AMD); *see also* Ex.1036, Regeneron (28-April-2008), 2). This creates blind spots in central vision and eventual scarring or formation of a disciform that represents the end-stage of AMD and associated vision loss.

49. As of 2009, it was reported that AMD "affects > 1.75 million individuals in the US and it is estimated that by 2020 this number will increase to almost 3 million," and "[w]orldwide, AMD is estimated to affect 14 million people." (Ex.1006, Dixon, 1573).

50. Early treatments for wet AMD were focused on laser and photodynamic therapy, in which portions of the eye were cauterized to prevent the spread of new

blood vessels. However, while this therapy could be effective at controlling vision loss in some patients, the therapy itself could result in vision loss in some portions of the eye. (*See* Ex.1043, Brown, 627; Ex.1006, Dixon, 1573 ("[Patients treated with photodynamic therapy] continued to experience a decline in visual acuity and the treatment was of questionable cost and effectiveness.")).

**2. Diabetic retinopathy (DR).**

51. DR "occurs when diabetes damages the tiny blood vessels in the retina, which is the light-sensitive tissue at the back of the eye." (Ex.1044, NIH DR, 1). DR "can cause blood vessels in the retina to leak fluid or hemorrhage (bleed), distorting vision." (*Id.*, 1-2). Further, "[i]n its most advanced stage, new abnormal blood vessels proliferate (increase in number) on the surface of the retina which can lead to scarring and cell loss in the retina." (*Id.*, 2). DR is the "leading cause of vision impairment and blindness among working-age adults." (*Id.*, 1).

**3. Diabetic macular edema (DME).**

52. DME is a consequence of DR. "DME is the build-up of fluid (edema) in a region of the retina called the macula." (Ex.1044, NIH DR, 3). "DME is the most common cause of vision loss among people with diabetic retinopathy." (*Id.*).

**B. Angiogenesis and Vascular Endothelial Growth Factor (VEGF).**

53. Angiogenesis is a key process necessary for embryonic development of the vascular system; early gene knockout studies revealed that loss of one or more

genes responsible for angiogenesis results in embryonic lethality. (*See* Ex.1045, Ferrara-1999, 1359). However, aberrant angiogenesis has also been identified as a contributor to the development of many tumors and disorders associated with increased vascularization. (*See id.*, 1360). Early on, researchers recognized the potential promise of targeting angiogenesis as a therapeutic strategy for treating diseases and disorders characterized by increased vascularity. (*See id.*, 1359-60).

**C. VEGF Antagonists.**

54. While VEGF may be "a naturally occurring protein in the body whose normal role is to trigger formation of new blood vessels (angiogenesis) to support the growth of the body's tissues and organs," (Ex.1036, Regeneron (28-April-2008), 2), additional research also identified a role for VEGF in tumor angiogenesis, with studies showing an upregulation of VEGF in various tumor types, (Ex.1046, Ferrara-2005, 968). As a result, anti-angiogenic VEGF inhibitors were identified as potential therapies, and were soon developed and entered clinical testing. (*Id.*, 971).

55. One of the first of these was bevacizumab, a humanized monoclonal antibody approved for the treatment of metastatic colon cancer in combination with 5-fluoruracil (5FU). (*Id.*, 967, 971).

56. VEGF has also been identified as a factor in the abnormal growth and fragility of new blood vessels in the eye, a condition associated with wet AMD. (*See id.*, 971-72; Ex.1012, Regeneron (28-April-2008), 2 ("Blockade of VEGF, which

can prevent abnormal blood vessel formation and vascular leak, has proven beneficial in the treatment of wet AMD and a VEGF inhibitor, ranibizumab, has been approved for treatment of patients with this condition.")). This led some physicians to suggest that bevacizumab and other anti-VEGF factors could be used to treat vitreoretinal diseases. Indeed, since the initial approval of bevacizumab for use in treating cancer, some ophthalmic physicians have used it off-label for the treatment of AMD (via intravitreal injection) with promising results. (*See, e.g.*, Ex.1047, Bashshur, 1).

57. In addition, based on the recognition that neovascularization and vascular leakage are a major cause of vision loss in wet AMD, anti-VEGF agents were also developed for the specific purpose of treating AMD.

58. One of these, ranibizumab, is a humanized monoclonal Fab fragment capable of blocking the activity of VEGF-A, and marketed under the name LUCENTIS®. Approved in 2006, it was originally indicated for the treatment of wet AMD via monthly intravitreal administration of 0.5 mg. The prescribing information available in 2006 also suggested a regimen of less frequent dosing following four monthly intravitreal injections. (Ex.1048, Lucentis PI, 1). Less frequent dosing was a preferred option due to the nature of intravitreal injections.

59. Intravitreal treatment involves administering an injection directly into the vitreous of the eye. Because of this, patients can experience significant pain and

discomfort. Soreness in the injected eye is a frequent side effect. In addition, potential complications that can occur include subconjunctival hemorrhage, infection, and inflammation. While the risk of infection is small, the consequences can be devastating. Lastly, the cost and inconvenience of monthly visits and injections can be a major drawback for patients, many of whom are elderly, cannot drive due to their deteriorating vision, and must rely on family, friends, or public transportation to get to their appointments—which can sometimes take 2-5 hours because of the assessments (OCT scan and visual acuity) that must be done, followed by the actual treatment, if necessary.

60. These drawbacks and risks were a recognized concern in the mid- and late-2000's. As a result, the frequency of injections was the subject of investigation for those of ordinary skill in the art at the time, as well as in the patient community, and the trend in the mid- to late-2000's already was moving away from monthly dosing. This is evident from the LUCENTIS® (ranibizumab) 2006 prescribing information ("treatment may be reduced to one injection every three months after the first four injections"), as well as the ranibizumab trials that post-date the early ANCHOR and MARINA monthly dosing trials, almost all of which were exploring ways to reduce injection frequency, including through *pro re nata*, i.e., as-needed, dosing schedules ("PRN"). (*See, e.g.*, SUSTAIN (PRN dosing after 3 monthly loading doses); EXCITE (quarterly dosing after 3 monthly loading doses); PrONTO

(PRN dosing after three monthly loading doses); SAILOR (PRN dosing after 3 monthly loading doses); and PIER (quarterly dosing after 3 monthly loading doses); Ex.1030, Mitchell, 6-7).

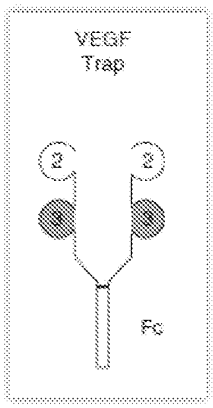
61. Also, in my experience, by 2010/2011 very few physicians were engaging in straight monthly dosing of VEGF antagonists. The typical practice was to either (1) treat with 2 or 3 monthly loading doses, followed by as-needed dosing thereafter, based on OCT and visual acuity assessments; or (2) engage in what has been termed "treat-and-extend," which involves 2 or 3 loading doses, followed by increased spacing between visits, so long as the patient is maintaining gains in visual acuity. (*See, e.g.*, Ex.1027, Spaide, 305; Ex.1049, Spielberg, 24).

62. Thus, those in the medical and research communities were actively investigating, and already incorporating, ways to reduce the time, expense, and patient discomfort associated with monthly intravitreal injections. (*See, e.g.*, Ex.1006, Dixon, 1574; Ex.1036, Regeneron (28-April-2008), 1 (noting that the long residence time of VEGF Trap-Eye in the eye means that the drug may be able to be dosed less frequently than once-monthly); Ex.1050, Schmidt-Erfurth, 1153 ("[The ranibizumab PrONTO study] suggested that flexible OCT-guided retreatment could sustain visual gain with fewer injections, a concept which has since become a popular model in clinical practice, particularly in Europe."); Ex.1051, Keane, 592

("[M]uch effort has focused on the development of alternative treatment regimens, which would reduce the number of injections required . . . .")).

**D. VEGF Trap-Eye/Aflibercept.**

63. VEGF Trap-Eye is a VEGF blocker developed by Regeneron. Unlike the VEGF blocker ranibizumab, which is a humanized monoclonal antibody, VEGF Trap-Eye is a fusion protein of Ig domain 2 of human VEGFR1 and Ig domain 3 of human VEGFR2 combined with a human IgG Fc fragment, as depicted below:




(Ex.1006, Dixon, 1575-76, Fig.1; *see also* Ex.1036, Regeneron (28-April-2008), 2 ("VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A along with the related Placental Growth Factor (PIGF).")).

64. In 2002, Regeneron published an article detailing its development of VEGF Trap-Eye, a high-affinity VEGF blocker "that has prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can

effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*," and was intended to treat disorders associated with increased angiogenesis. (Ex.1004, Holash, 11393).

65. From this, the authors concluded that "although the parental VEGF-Trap and its VEGF-Trap$_{R1R2}$ derivative are quite comparable *in vitro* (see above), the VEGF-Trap$_{R1R2}$ performs much better *in vivo*, presumably because of its dramatically enhanced pharmacokinetic profile." (*Id.*, 11395-96).

66. The authors closed with a report of studies comparing VEGF-Trap$_{R1R2}$ with anti-VEGF monoclonal antibodies, and concluded that efficacy of VEGF Trap was equal to or better than anti-VEGF antibodies. This led the authors to conclude that the efficacious dose of the VEGF Trap may be lower than that of a monoclonal anti-VEGF antibody. (*See id.*, 11397).

67. The Holash authors concluded that VEGF Trap may be useful in the treatment of retinopathies, given the contribution of pathological angiogenesis to such disorders. (*See id.*).

68. This is consistent with the understanding of physicians at the time that VEGF Trap-Eye was known to have a high binding affinity to VEGF, which the medical community believed could translate to good clinical efficacy outcomes.

69. Subsequent work by Regeneron reinforced VEGF Trap's potential as a possible antiangiogenic therapy for vascular eye diseases. For example, Rudge

noted that blocking VEGF-A exhibited impressive results in the treatment of wet AMD, suggesting that a VEGF blockade like VEGF Trap could be useful in treating eye disorders characterized by leaky and proliferating vasculature. (Ex.1052, Rudge, 411).

70. Rudge also includes experimental work which indicated a role for VEGF in the pathology of other vascular eye disorders, including diabetic edema, DR, and AMD. (*Id.*, 414). Preclinical studies with VEGF Trap showed that it was able to inhibit choroidal and corneal neovascularization, suppress vascular leak in the retina, and promote the survival of corneal transplants by inhibiting neovascularization. (*Id.*). Following the promising preclinical trials, VEGF Trap entered clinical trials assessing its effectiveness in treating AMD and diabetic edema and retinopathy. The preliminary results showed that "VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity." (*Id.*, 414-15; *see also* Ex.1088, Nguyen-2006, 1522). The authors also noted that the VEGF Trap was in the process of entering even more clinical trials related to vascular eye diseases. (Ex.1052, Rudge, 415).

**E. Regeneron's Press Releases and Clinical Trials.**

71. In the mid-2000's, Regeneron began reporting on its clinical trials of VEGF Trap-Eye in AMD patients. Provided below is a table summarizing the trials, their nomenclature, exemplary dosing regimens involved, and some of the references

that refer to those studies, which will be discussed in greater detail later in my declaration.

| Trial | Name | Reference(s) | Dosing Regimen |
|---|---|---|---|
| Phase 1 (AMD) | CLEAR-IT 1 | Dixon; Nguyen-2009 | Single intravitreal dose (incl. 0.5, 2, and 4 mg doses) |
| Phase 2 (AMD) | CLEAR-IT 2 | Dixon; Adis | Monthly or quarterly through week 12 followed by PRN (incl. 0.5, 2, and 4 mg doses) |
| Phase 3 (AMD) | VIEW1; VIEW2 | Dixon; Adis; NCT-795; NCT-377; Regeneron (8-May-2008)[3] | Monthly through week 8, followed by every 8 weeks (0.5 and 2 mg doses) |

[3] The VIEW1 and VIEW2 trials were discussed in numerous Regeneron press releases between August 2007 and the time the '338 patent priority applications were filed in 2011. Regeneron (8-May-2008) is provided here as an illustrative example.

72. In addition, because some of the AMD clinical trials involving ranibizumab (LUCENTIS®) are discussed throughout my declaration, and the dosing regimens used in those studies are relevant to the dosing regimen used in Regeneron's Phase 3 VIEW1/2 studies of VEGF Trap-Eye, a table summarizing those studies is also provided:

| Trial[4] | Dosing Regimen |
|---|---|
| MARINA (AMD) | Monthly |
| ANCHOR (AMD) | Monthly |
| PIER (AMD) | Quarterly after 3 initial monthly injections |
| EXCITE (AMD) | Quarterly after 3 initial monthly injections |
| PrONTO (AMD) | PRN after 3 initial monthly injections |
| SAILOR (AMD) | PRN after 3 initial monthly injections |
| SUSTAIN (AMD) | PRN after 3 initial monthly injections |

73. In connection with Regeneron's VEGF Trap clinical program, Regeneron issued a series of press releases, beginning around 2007, disclosing, in

[4] A summary of these trials also can be found in Ex.1035, Mitchell.

sum, the following information regarding its clinical trials to persons of ordinary skill in the art:

| Press Release | Representative Disclosure |
|---|---|
| 27 Mar. 2007 (Ex.1053) | **Phase 2 trial**: 4-week (i.e., monthly) dosing with VEGF Trap-Eye yields "a statistically significant reduction in retinal thickness after 12 weeks." (Ex.1053, Regeneron (27-March-2007), 1). |
| 2 Aug. 2007 (Ex.1054) | **Phase 2 trial**: Results show monthly (i.e., every 4 week) VEGF Trap-Eye dosing yields "a statistically significant reduction in retinal thickness and improvement in visual acuity after 12 weeks." (Ex.1054, Regeneron (2-August-2007), 1).<br>**Phase 3 trial**: VIEW1 trial initiated, testing the safety and efficacy of VEGF Trap-Eye dosed at either 4 week intervals (0.5 and 2.0 mg) or 8 week intervals (2.0 mg). (*Id.*). |
| 28 Apr. 2008 (Ex.1036) | **Phase 2 trial**: Previously reported gains in visual acuity and decreases in retinal thickness for week 12 were maintained out to week 32 when using a PRN (i.e., *pro re nata* or as-needed) dosing schedule after week 12. (Ex.1036, Regeneron (28-April-2008), 1). |

| Press Release | Representative Disclosure |
|---|---|
| | **Phase 3 trials (VIEW1 & 2)**: Testing "a monthly loading dose of 0.5 mg or 2.0 mg for 12 weeks, followed by a nine-month fixed-dosing regimen of 0.5 mg monthly, 2.0 mg monthly, or 2.0 mg every eight weeks." (*Id.*, 2). |
| 8 May 2008 (Ex.1013)[5] | **Phase 3 trials (VIEW1 & 2)**: Evaluating "2.0 mg [VEGF Trap-Eye] at an 8-week dosing interval, including one additional 2.0 mg dose at week four," for up to one year—i.e., doses at weeks 0, 4, 8, 16, 24, 32, 40, and 48. (Ex.1013, Regeneron (8-May-2008), 1). |
| 19 Aug. 2008 (Ex.1089) | **Phase 2 trial**: Patients receiving monthly doses of either 2.0 or 0.5 mg VEGF Trap-Eye for 12 weeks followed by PRN dosing achieved improved visual acuity and decreased retinal thickness after one year. (Ex.1089, Regeneron (19-August-2008), 1). **Phase 3 trials (VIEW1 & 2)**: Studies involve "2.0 mg [VEGF Trap-Eye] every 8 weeks (following three monthly doses)"— |

[5] The same information was reported by Regeneron's partner, Bayer, in their own press release, dated the same day. (*See, e.g.*, Ex.1032, Bayer (8-May-2008)).

| Press Release | Representative Disclosure |
|---|---|
| | i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48. (*Id.*). |
| 28 Sept. 2008 (Ex.1056) | **Phase 2 trial**: Patients receiving monthly doses of either 2.0 or 0.5 mg VEGF Trap-Eye for 12 weeks followed by PRN dosing achieved improved visual acuity and decreased retinal thickness after one year.[6] (Ex.1056, Regeneron (28-September-2008), 1). **Phase 3 trials (VIEW1 & 2)**: Studies involve "2.0 mg [VEGF Trap-Eye] every 8 weeks (following three monthly doses)"—i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48.[7] (*Id.*, 2). |

[6] The September 28, 2008 Press Release also reported that the Phase 2 results were presented earlier that day at the 2008 annual meeting of the Retina Society in Scottsdale, AZ, and that slides, including data reported at the meeting, were available at the Regeneron website.

[7] The Phase 3 VIEW1 and VIEW2 studies reported in the above disclosures appear to correspond to the Phase 3 study reported in the '338 patent at Example 4. (*Compare* Ex.1056, Regeneron (28-September-2008), 2, *with* Ex.1001, '338 patent, 9:10 – 13:48).

| Press Release | Representative Disclosure |
|---|---|
| | |
| 14 Sep. 2009<br><br>(Ex.1068) | **Phase 3 trials (VIEW1 & 2)**: Treatment arms for the first year of the VIEW studies to be (i) 0.5 mg every four weeks; (ii) 2.0 mg every four weeks; and (iii) 2.0 mg every eight weeks following three monthly doses—i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48. PRN dosing to be used for the second year of the programs. (Ex.1068, Regeneron (14-September-2009), 1). |

## VII. SCOPE AND CONTENT OF THE PRIOR ART REFERENCES.

### A. Dixon (Ex.1006).

74. Dixon was published in 2009. I understand that because Dixon published before the earliest priority date of the '338 patent,[8] it is prior art. I have reviewed Dixon. Dixon is an article summarizing the current state of AMD therapies

[8] I have been asked by counsel for Mylan to use January 13, 2011, as the priority date of the '338 patent for purposes of my declaration. I understand that counsel for Mylan reserves the right to challenge whether there is sufficient support in the priority document for Regeneron to properly rely on this date.

as of 2009, and profiling in particular, the development and clinical testing of Regeneron's VEGF Trap-Eye, including the details of Regeneron's VIEW Phase 3 dosing regimen. The following paragraphs represent examples of the disclosures in Dixon that, in my opinion, are relevant to the method(s) of treatment claimed in the '338 patent:

75. As an initial matter, Dixon discloses that "[i]n addition to two anti-VEGF drugs currently in widespread use, ranibizumab and bevacizumab, a number of medications that interrupt angiogenesis are currently under investigation." (Ex.1006, Dixon, 1573).

76. To that end, Dixon reports on several ranibizumab studies, including the PIER and PrONTO studies initiated by Genentech in 2004, which, according to Dixon, were intended to study alternative dosing schedules that might reduce the "time and financial burden of monthly injections." (*Id.*, 1574).

- The PIER study assessed patients after receiving 3 monthly (i.e., every 4 week) injections, followed by quarterly (i.e., every 12 week) dosing.
- The PrONTO study assessed patients after receiving 3 monthly (i.e., every 4 week) injections, followed by as needed (p.r.n.) dosing. The PrONTO study reported that "78% of patients had maintained vision and vision had improved by > 3 lines in 43% of patients with an average of five injections a year." (*Id.*).

77. While acknowledging the efficacious outcomes achieved with ranibizumab and bevacizumab, Dixon states that in the development of new drugs for treating AMD, the focus was on improving efficacy and extending the duration of action, and thus, allowing for less frequent dosing.[9] (*Id.*). Regeneron's VEGF Trap-Eye—which, at the time, was well known and in commercial development for the treatment of AMD—was identified by Dixon as "[o]ne promising new drug" that "blocks all isoforms of VEGF-A and placental growth factors-1 and -2." (*Id.*, 1573).

78. Among other VEGF Trap related disclosures,[10] Dixon discusses Regeneron's Phase 2 trial, named CLEAR-IT-2. (*Id.*, 1576). The CLEAR-IT-2 trial included 5 dose groups:

- 0.5 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8, and 12);

---

[9] This was a logical benefit. As I mention elsewhere in this declaration, physicians and patients were interested in reducing the frequency of dosing of anti-VEGF agents given, among other things, the unpleasantness of intravitreal injections.

[10] For example, Dixon discusses (i) Regeneron's CLEAR-IT-1 trial, a two-part, Phase 1 study of intravitreal aflibercept in patients with AMD; and (ii) "a small open-label safety study for the treatment of diabetic macular edema" with a single dose of 4 mg VEGF Trap.

- 2.0 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8, and 12);
- 0.5 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12);
- 2.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12); and
- 4.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12). (*Id.*).

Following each of the above fixed dosing regimens, "patients were treated with the same dose of VEGF Trap-Eye on a p.r.n. [i.e., as needed][11] basis." (*Id.*).

79. Dixon states that in the Phase 2 CLEAR-IT-2 trial, "[p]atients initially treated with 2.0 or 0.5 mg of VEGF Trap-Eye monthly achieved mean improvements of 9.0 ($p < 0.0001$) and 5.4 ($p < 0.085$) ETDRS letters with 29 and 19% gaining, respectively, $\geq$ 15 ETDRS letters at 52 weeks." (*Id.*). Dixon also states that "[d]uring the p.r.n. dosing period, patients initially dosed on a 2.0 mg monthly schedule received an average of 1.6 more injections and those initially dosed on a 0.5 mg monthly schedule received an average of 2.5 injections." (*Id.*).

[11] In my experience, PRN dosing at this stage in any such dosing regimen involves monthly visits wherein each patient is evaluated and a determination is made (on a monthly basis) whether another injection is required. Consequently, in my opinion, the most frequent dosing that would typically occur under such a "p.r.n. basis" is monthly (or every 4 weeks).

80. Dixon also reported on Regeneron's Phase 3 AMD studies, named VIEW1 and VIEW2, which were intended to "evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (*Id.*). The planned dosing regimens included:

- 0.5 mg every 4 weeks (i.e., doses at weeks 0, 4, 8, 12, . . .);
- 2.0 mg every 4 weeks (i.e., doses at weeks 0, 4, 8, 12, . . .); and
- 2.0 mg every 8 weeks *after 3 initial, monthly doses* (i.e., doses at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, 48 . . .). (*Id.*).

Also included as a comparator was 0.5 mg of ranibizumab administered every 4 weeks (i.e., monthly). (*Id.*). Furthermore, "[a]fter the first year of the study, patients will enter a second year of p.r.n. dosing evaluation." (*Id.*). The choice of every eight weeks, or bimonthly dosing, for the VIEW trials is consistent with Dixon's stated concerns among physicians about the time and financial burdens of monthly administration required for existing therapies, like ranibizumab, and the suggestion that "desirable attributes for emerging therapies for neovascular AMD include higher visual improvement rates and *decreased dosing intervals*." (*Id.*, 1577 (emphasis added)).

81. The Dixon authors also noted that "VEGF Trap-Eye is under Phase II investigation in DME and Phase III investigation in central retinal vein occlusion [RVO]" and suggested that "FDA approval of VEGF Trap-Eye for these indications

would significantly add to the ophthalmologists' armamentarium for treatment of retinal vascular disease." (*Id.*, 1577-78).

82. Lastly, I note that much of Dixon's information about Regeneron's Phase 3 VIEW studies was derived from online records from clinicaltrials.gov—the same records that I discuss in this declaration. (*See id.*, 1579, (Ref. Nos. 46-47 (citing NCT00509795, accessed Sep. 28, 2008, and NCT00637377, also accessed Sep. 28, 2008))).

**B. Adis (Ex.1007).**

83. The Adis reference was published in 2008. I understand because the Adis reference published before January 13, 2011, the earliest priority date of the '338 patent, it is prior art.

84. Adis discloses that "[a]flibercept is a fully human recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third Ig domain of VEGFR2, fused to the Fc region of human $IgG_1$," and that while Regeneron and Sanofi were developing it for the treatment of cancer, Regeneron and Bayer were developing it for eye disorders. (Ex.1007, Adis, 261). Throughout Adis, the authors use the terms aflibercept and VEGF Trap-Eye interchangeably. (*See, e.g., id.*, Title).

85. Adis states that "Regeneron and Bayer initiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD in August 2007." (*Id.*, 263).

86. According to Adis, the VIEW1 and VIEW2 trials were initiated to evaluate the safety and efficacy of (1) 0.5 and 2.0 mg doses administered monthly (i.e., at weeks 0, 4, 8, 12, 16 . . .); or (2) 2.0 mg doses administered every 8 weeks following three monthly doses (i.e., at weeks 0, 4, 8, 16, 24, 32, 40, and 48). (*Id.* ("2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4.")).[12]

87. Adis also discusses Regeneron disclosures indicating that "Regeneron has completed a 12-week, phase II trial in patients with wet AMD, to evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens." (*Id.*). Adis states that these dosing regimens were:

- 0.5 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8 and 12);
- 2.0 mg monthly for 12 weeks (i.e., doses at weeks 0, 4, 8. and 12);
- 0.5 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12);
- 2.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12); and
- 4.0 mg quarterly for 12 weeks (i.e., doses at weeks 0 and 12). (*Id.*).

[12] Notably, Adis cites Regeneron and Bayer Press Releases retrieved online from the companies' respective websites. (*Id.*, 263, 268, Ref. Nos. 10-13). In my opinion, this confirms that such press releases were well known and widely available to persons of ordinary skill in the art prior to January 2011.

88. Adis also covers the Phase 2 AMD trial results, reporting that at the 32-week point, "157 patients receiving either 0.5 or 2.0 mg followed by as-needed (PRN) dosing achieved mean improvements in visual acuity of 8.0 and 10.1 letters, respectively, and mean decreases in retinal thickness of 141 and 162 microns, respectively." (*Id.*, 267). The authors continue, noting that over the 20 weeks following the 12-week loading dose period, patients only required on average one additional injection "to maintain visual acuity gain achieved," and observing that while PRN dosing following fixed quarterly dosing maintained improvements, it was not as robust as those results achieved with initial fixed monthly dosing. (*Id.*, 268). They also report that Phase I AMD preliminary results "have shown rapid, substantial and prolonged (≥ 4 weeks) reductions in retinal thickness with single-dose intravitreal injections of VEGF Trap." (*Id.*).

89. Lastly, I note that much of Adis' information about Regeneron's Phase 2 CLEAR-IT-2 and Phase 3 VIEW studies was derived from Regeneron and Bayer press releases—some of which are the same press releases that I discuss in this declaration. (*See id.*, Ref. Nos. 10-16).

### C. Regeneron (8-May-2008) (Ex.1013).

90. Regeneron (8-May-2008) is dated May 8, 2008. Because Regeneron (8-May-2008) published[13] before January 13, 2011, the earliest priority date of the '338 patent, it is my understanding that Regeneron (8-May-2008) qualifies as prior art to the '338 patent.

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[13] I was also asked whether, in my opinion, Regeneron (8-May-2008) was publicly available to persons of ordinary skill in the art prior to January 13, 2011. In my opinion, accessing records such as Regeneron (8-May-2008) is a task consistent with the exercise of reasonable diligence and would have involved little more than calling up Regeneron's website and clicking on the press releases kept therein. Furthermore, in my opinion, Regeneron's press releases at this time were well known and widely available to persons of ordinary skill in the art of treating angiogenic eye disorders. Indeed, I am aware of several colleagues who reviewed such press releases prior to January 2011. For example, Adis (Ex.1007) cited to over 15 Regeneron and Bayer press releases in its 2008 discussion of aflibercept (VEGF Trap-Eye), confirming, in my opinion, the public availability and widespread dissemination of Regeneron (8-May-2008). In sum, it is my opinion that Regeneron (8-May-2008) was unequivocally available publicly to persons of ordinary skill in the art prior to January 13, 2011.

91. Regeneron (8-May-2008) reports on the commencement of the second Phase 3 trial (VIEW2) for evaluating the safety and efficacy of VEGF Trap-Eye in treating AMD. (Ex.1013, Regeneron (8-May-2008), 1). The VIEW2 trial was intended to evaluate patients enrolled from Europe, Asia Pacific, Japan, and Latin America, and was described as a "confirmatory Phase 3 trial" to follow positive Phase 2 results that showed VEGF Trap-Eye was able to reduce retinal thickness and improve visual acuity. (*Id.*). Dr. Yancopoulos, CEO of Regeneron and sole inventor on the '338 patent, was quoted as touting the need to provide "optimal care to those patients with wet AMD" and to evaluate "different dosing regimens." (*Id.*). Those dosing regimens were to include:

- 0.5 mg every 4 weeks (i.e., monthly);
- 2.0 mg every 4 weeks (i.e., monthly); and
- 2.0 mg every eight weeks (i.e., bimonthly) with an additional dose at week 4 (in other words, three monthly doses followed by bimonthly dosing). (*Id.*).

Following the first year of dosing according to the above regimens, the second year will incorporate a "flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but not more often than every 4 weeks." (*Id.*).

92. Regeneron (8-May-2008) also reports on the results of the Phase 2 trial, disclosing that at 12 weeks "VEGF Trap-Eye met both primary and secondary key

endpoints: a statistically significant reduction in retinal thickness . . . and a statistically significant improvement from baseline in visual acuity." (*Id.*). They further disclosed that following the 12-week fixed dosing loading phase of the trial, patients were treated on a PRN/as-needed basis, and reported that the PRN dosing, through week 32, "maintained the gain in visual acuity and decrease in retinal thickness achieved at week 12." (*Id.*).

**D. NCT-795 (Ex.1014).**

93. NCT-795 is an online record from the site clinicaltrials.gov, a database of clinical trial information developed by the National Library of Medicine and a service of the U.S. National Institutes of Health.

**1. ClinicalTrials.gov.**

94. Clinicaltrials.gov is a website publicly accessible to anyone, including physicians, patients, and researchers, interested in viewing information pertaining to clinical trials being conducted in the United States and abroad [available since at least 2000]:

> ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions. NIH and the Food and Drug Administration (FDA) worked together to develop the site, which was made available to the public in February 2000.

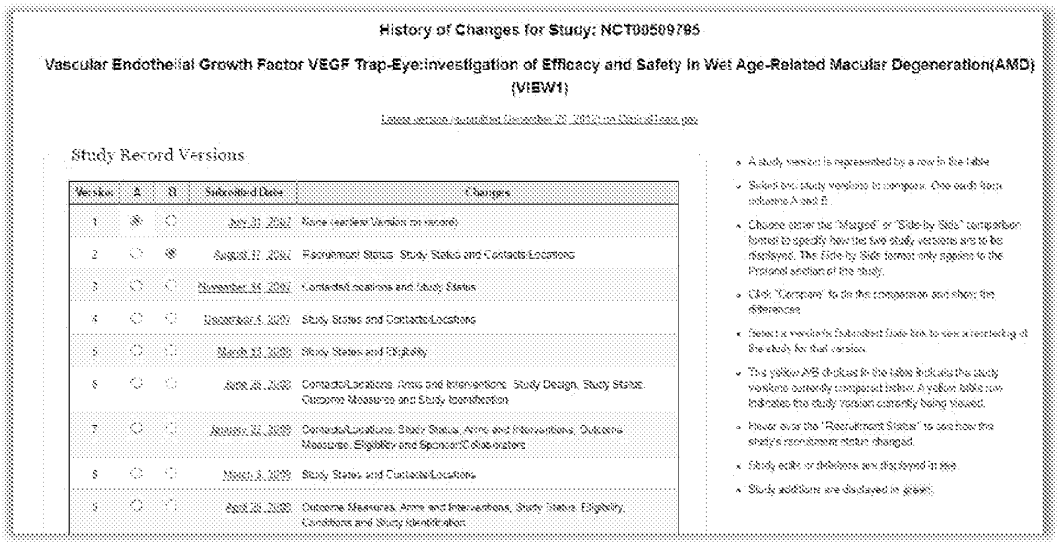
95. I am, and have been throughout the majority of my clinical career, aware of clinicaltrials.gov as a valuable online resource for learning about the latest

clinical trials involving drugs for the treatment of retinovitreal eye disorders. In fact, the first time I posted clinical trial data to clinicaltrials.gov was in 2009.

96. I am also aware that clinicaltrials.gov maintains an archive site, found at the link "History of Changes" in each NCT clinical trial record, e.g.:

| | |
|---|---|
| Responsible Party: | Regeneron Pharmaceuticals |
| ClinicalTrials.gov Identifier: | NCT00509795 History of Changes |
| Other Study ID Numbers: | VGFT-OD-0605 |
| First Posted: | August 1, 2007 Key Record Dates |
| Results First Posted: | April 18, 2012 |
| Last Update Posted: | December 28, 2012 |
| Last Verified: | December 2012 |

97. I understand that this "History of Changes" site maintains updates to each clinical trial record, and that these updates can be retrieved from the online archive site with the date on which the update occurred indicated in the file record, along with a comparison showing changes that were made since the previous update. A partial snapshot of this portion of the "History of Changes" page is shown here:



History of Changes for Study: NCT00509795

Vascular Endothelial Growth Factor VEGF Trap-Eye:Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration(AMD) (VIEW1)

Latest version submitted December 20, 2012 on ClinicalTrials.gov

Study Record Versions

| Version | A | B | Submitted Date | Changes |
|---|---|---|---|---|
| 1 | ◉ | ○ | June 21, 2007 | None (earliest Version on record) |
| 2 | ○ | ◉ | August 17, 2007 | Recruitment Status, Study Status and Contacts/Locations |
| 3 | ○ | ○ | November 14, 2007 | Contacts/Locations and Study Status |
| 4 | ○ | ○ | December 5, 2007 | Study Status and Contacts/Locations |
| 5 | ○ | ○ | March 13, 2008 | Study Status and Eligibility |
| 6 | ○ | ○ | June 26, 2008 | Contacts/Locations, Arms and Interventions, Study Design, Study Status, Outcome Measures and Study Identification |
| 7 | ○ | ○ | January 30, 2009 | Contacts/Locations, Study Status, Arms and Interventions, Outcome Measures, Eligibility and Sponsor/Collaborators |
| 8 | ○ | ○ | March 3, 2009 | Study Status and Contacts/Locations |
| 9 | ○ | ○ | April 28, 2009 | Outcome Measures, Arms and Interventions, Study Status, Eligibility, Conditions and Study Identification |

- A study version is represented by a row in the table.
- Select two study versions to compare. One each from columns A and B.
- Choose either the "Merged" or "Side by Side" comparison format to specify how the two study versions are to be displayed. The Side by Side format only applies to the Protocol section of the study.
- Click "Compare" to do the comparison and show the differences.
- Select a version's Submitted Date link to view a printable of the study for that version.
- The yellow AVS displayed in the table indicates the study versions currently compared below. A yellow table row indicates the study version currently being viewed.
- Hover over the "Recruitment Status" to see how the study's recruitment status changed.
- Study edits or deletions are displayed in red.
- Study additions are displayed in green.

98. I further understand that the "Submitted Date" column indicates the date on which the updated information was provided to clinicaltrials.gov and thus the date on or about which the information was publicly accessible from the database.

99. In sum, it is my firm opinion that clinicaltrial.gov records (including archives and updates) were well known and widely available to persons of ordinary skill in the art prior to January 2011. I myself regularly searched for and consulted records in the clincialtrials.gov database before 2011 and continue to do so today. The consultation of clinicaltrials.gov is a regular aspect of the research that I do in assessing the safety and efficacy of new drugs, and in my experience, many of my colleagues who treat angiogenic eye disorders regularly consult the online records

of clinicaltrials.gov as well. My opinion regarding the public availability of NCT-795, specifically, is further confirmed by prior art references to the '338 patent, which cite to NCT-795 (as obtained from clinicaltrials.gov), as well as several other clinicaltrials.gov records. (*See, e.g.*, Ex.1006, Dixon, 1576, 1579).[14]

**2. NCT-795 discloses the VIEW1 regimen.**

100. NCT-795 was originally submitted on July 31, 2007. (*See, e.g.*, Ex.1014, NCT-795, 1, 3). NCT-795 describes the VIEW1 study as a Phase 3 randomized double-masked safety and efficacy study of intravitreal VEGF Trap-Eye in the treatment of neovascular age-related macular degeneration (wet AMD). (*Id.*, 3-4). The record also states that the primary outcome measure will be visual acuity changes compared to baseline, and that the study is anticipated to involve about 1200 patients in the U.S. and Canada. (*Id.*, 4, 9).

101. I have used the archive document that compares the April 28, 2009 version to the March 3, 2009 version. The description at the top of the page indicates that the April 28, 2009 version is "v9" and the March 3, 2009 version is "v8." The record indicates that changes made from March 3, 2009 to April 28, 2009 are

[14] Citations to the clinicaltrials.gov records for NCT00509795 and/or NCT00637377 can also be found in other publications before 2011. (*See, e.g.*, Ex.1073, Anderson, 275; Ex.1074, Ciulla, 162; Ex.1075, Ni, 403, 409; Ex.1076, Zarbin, 1360).

displayed in a "merged" format, and I understand from the document that additions are indicated in green, while deletions or edits are displayed in red strikethrough. (*Id.*, 1-2).

102. The April 28, 2009 update provides the specific dosing regimens for each VIEW treatment arm. (Ex.1014, NCT-795, 5-8). The April 28, 2009 record states that April 28, 2009 was the date the update was submitted and April 29, 2009 the date it was posted. (*Id.*, 4). From my experience using, and my knowledge of, the site and how it works and archives information, I understand that to mean that the information displayed on that page and the subsequent pages, would have been the information available to researchers on or about April 29, 2009. Therein, the record indicates that patients will be randomly assigned to one of four treatment regimens:

- 2 mg VEGF Trap-Eye every 4 weeks (2Q4);
- 0.5 mg VEGF Trap-Eye every 4 weeks (0.5Q4);
- 2 mg VEGF Trap-Eye every 8 weeks (2Q8); and
- 0.5 mg ranibizumab every 4 weeks (RQ4). (*Id.*, 5-7).

103. The record also states that experimental arm 3 will include "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year":

| Assigned Interventions |
| --- |
| *Drug: VEGF Trap-Eye*<br>*2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks* |

(*Id.*, 8). In other words, subjects in the 2Q8 treatment arm were to receive 2 mg injections at weeks 0, 4, 8, 16, 24, 32, etc. (i.e., 3 monthly loading doses, followed by every-eight-week dosing). The April 28, 2009 record also states that the primary outcome measure will be "[t]he proportion of subjects who maintain vision at Week 52, where a subject is classified as maintaining vision if the subject has lost fewer than 15 letters on the ETDRS chart compared to baseline (i.e. prevention of moderate vision loss)." (*Id.*, 9). The record also notes that the timeframe for this assessment will be "Week 52." (*Id.*).

**E. NCT-377 (Ex.1015).**

104. NCT-377 is an online record from the site clinicaltrials.gov, a database of clinical trial information developed by the National Library of Medicine and a service of the U.S. National Institutes of Health. As stated above, clinicaltrials.gov is a website publicly accessible to anyone, including physicians, patients, and researchers, interested in viewing information pertaining to clinical trials being conducted in the United States and abroad. My statements above regarding NCT

records and my opinion regarding their availability to persons of ordinary skill in the art apply equally to this record, NCT-377.

105. My opinion regarding the public availability of NCT-377, specifically, is further confirmed by prior art to the '338 patent, which cite to NCT-377 (as obtained from clinicaltrials.gov) as well as several other clinicaltrials.gov records. (*See, e.g.*, Ex.1006, Dixon, 1576, 1579).[15]

106. NCT-377 indicates that the earliest version of NCT-377 was submitted on March 17, 2008, and first posted March 18, 2008. (Ex.1015, NCT-377, 1, 4). From my experience using, and my knowledge of, the site and how it works and archives information, I understand that to mean that the information displayed on that page and the subsequent pages, would have been the information available to online observers on or about March 17-18, 2008. (*See, e.g.*, *id.* ("First Submitted that Met QC Criteria: March 17, 2008"; "First Posted: March 18, 2008")). The March 17, 2008 record describes the VIEW2 study as a "phase III, double-masked, randomized, study of the efficacy and safety of VEGF Trap-Eye in patients with neovascular age-related macular degeneration" and further states that "[a]pproximately 1200 patients will be randomized in Europe, Asia, Japan, Australia and South America." (*Id.*, 5).

[15] *See supra* note 15.

107. The NCT-377 record also lists 4 treatment arms, or interventions, for the VIEW2 study, including Arm 3:

| Arms | Assigned Interventions |
|---|---|
| Experimental: Arm 3 | Drug: VEGF Trap-Eye<br>2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. |

(*Id.*, 6). The additional 2.0 mg dose at week 4 means that 2.0 mg doses were to be administered at weeks 0, 4, and 8, followed by doses at weeks 16, 24, 32, 40, and 48.

108. Additional treatment arms of the VIEW2 study included:

- **Arm 1:** 0.5 mg every 4 weeks during the first year (i.e., doses at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). Thereafter doses as frequently as every 4 weeks but no less frequently than every 12 weeks;
- **Arm 2:** 2.0 mg every 4 weeks during the first year (i.e., doses at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). Thereafter doses as frequently as every 4 weeks but no less frequently than every 12 weeks; and
- **Arm 4:** 0.5 mg ranibizumab every 4 weeks during the first year (i.e., doses at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52). Thereafter

doses as frequently as every 4 weeks but no less frequently than every 12 weeks. (*Id.*, 6).

109. Subsequent updates were made and archived between April 2008 and November 2014. (*Id.*, 1-3). However, the dosing regimens remained unchanged from the original throughout these subsequent updates.

**F. '664 Patent (Ex.1009).**

110. U.S. Patent No. 7,396,664 issued July 8, 2008, from Application No. 11/204,709, filed on August 16, 2005, and is assigned, on its face, to Regeneron Pharmaceuticals, Inc. I understand that the '664 patent qualifies as prior art to the '338 patent because it issued prior to January 13, 2011, the earliest priority date of the '338 patent.

111. The '664 patent is drawn to VEGF Traps that "are therapeutically useful for treating VEGF-associated conditions and diseases," (Ex.1009, '664 patent, Abstract), specifically, "eye disorders such as macular degeneration and diabetic retinopathy," (*id.*, 2:64 – 3:12).

112. The '664 patent states that the invention includes "a fusion polypeptide comprising receptor components R1-R2-F, wherein R1 is vascular endothelial cell growth factor (VEGF) receptor component Ig domain 2 of Flt-1 (Flt1D2), R2 is VEGF receptor component Ig domain 3 of Flk-1 (Flk1D3) (also known as KDR), and F is a fusion component." (*Id.*, 1:36-42). Further, "[i]n a preferred embodiment,

R1 and R2 are the only receptor components present. In a specific embodiment, the VEGF-binding fusion polypeptide is amino acids 27-129 (R1) and 130-231 (R2) of SEQ ID NO:8, or a variant thereof." (*Id.*, 1:47-51).

113. Moreover, the '664 patent states that "[t]he fusion component F is selected from the group consisting of a multimerizing component, a serum protein, or a molecule capable of binding a serum protein" and that "[p]referably, the multimerizing component is an immunoglobulin domain." (*Id.*, 1:52-54, 64-65). The '664 patent specifies that one embodiment of "F is a full-length or truncated immunoglobulin domain consisting of amino acids 232-458, 232-457, or 352-458 of SEQ ID NO:8." (*Id.*, 1:65-67). The '664 patent continues, stating that "a signal sequence (S) may be included at the beginning (or N-terminus) of the fusion polypeptide of the invention." (*Id.*, 2:28-30). Further, in a specific embodiment, "the fusion polypeptide of the invention expressed in a mammalian cell line such as a CHO cell comprises amino acids 27-457 of SEQ ID NO:8." (*Id.*, 2:53-55).

**G. '758 Patent (Ex.1010).**

114. U.S. Patent No. 7,374,758 issued May 20, 2008, from Application No. 11/016,503, filed on December 17, 2004, and is assigned, on its face, to Regeneron Pharmaceuticals, Inc. I understand that the '758 patent qualifies as prior art to the '338 patent because it issued prior to January 13, 2011, the earliest priority date of the '338 patent.

115. The '758 patent is drawn to "[m]odified chimeric polypeptides with improved pharmacokinetics" and methods of "using the modified polypeptides to decrease or inhibit plasma leakage and/or vascular permeability in a mammal." (Ex.1010, '758 patent, Abstract). The '758 patent discloses the VEGF fusion polypeptide disclosed as preferred embodiments in the '664 patent discussed above. Specifically, the '758 patent sets forth in Figure 24A-C the annotated sequence of VEGFR1R2-FcΔC1(a), which includes the signal sequence (aa 1-26); the Flt-1 Ig domain 2 (aa 27-129); the Flk-1 Ig domain 3 (aa 130-231); and the Fc domain (aa 232-458). (*Id.*, Fig.24A-C; *see also id.*, 10:15-17 ("Nucleotide (SEQ ID NO:15) and deduced amino acid sequence (SEQ ID NO:16) of the modified Flt1 receptor termed VEGFR1R2-FcΔC1(a).")).

**H. Dix (Ex.1033).**

116. U.S. Publication No. 2006/0217311 ("Dix") was published September 28, 2006, from Application No. 11/387,256, filed March 22, 2006. Because Dix published before January 13, 2011, the earliest priority date of the '338 patent, it is my understanding that Dix qualifies as prior art to the '338 patent.

117. Dix is drawn to "[f]ormulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist" wherein "[p]referably, the fusion protein has the sequence of SEQ ID NO:4." (Ex.1033, Dix, Abstract). I note that SEQ ID NO:4 of Dix is the same as that of SEQ ID NO:2 of the '338 patent.

118. Dix discloses that "[a] soluble VEGF-specific fusion protein antagonist, termed a 'VEGF trap' has been described [in Kim (Ex.1090) and Holash (Ex.1004)], which applications are specifically incorporated by reference in their entirety." (*Id.*, [0005]). Dix describes the fusion protein as containing the second Ig domain of Flt1, the third Ig domain of Flk1, and a multimerizing component, and more specifically, where the fusion protein has the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4. (*Id.*, [0008]). More preferred embodiments consist of formulations containing the fusion protein with the amino acid sequence of SEQ ID NO:4. (*Id.*, [0013]-[0014]). Furthermore, a specific embodiment includes a fusion protein comprising amino acids 27-457 of SEQ ID NO:4. (*Id.*, [0030]).

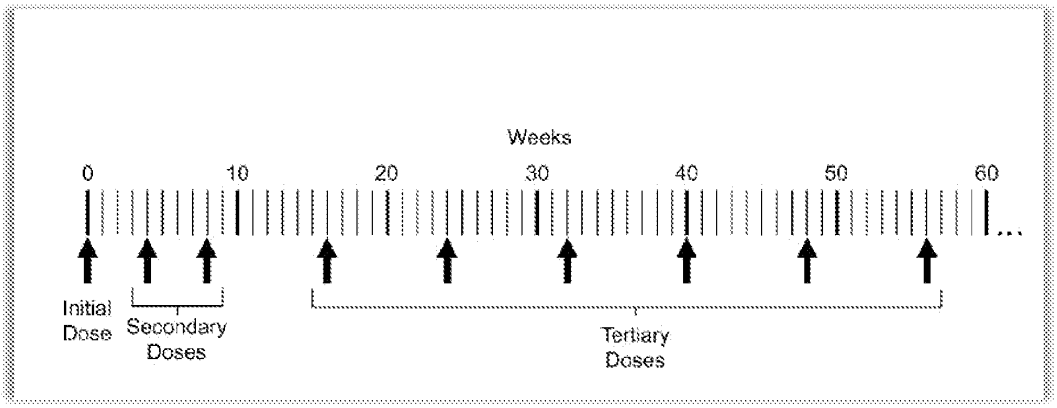
## VIII. UNPATENTABILITY OF THE '338 PATENT.

### A. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by Dixon (Ex.1006).

119. I was asked to review the challenged claims of the '338 patent and compare them to the disclosures of Dixon. It is my opinion that Dixon discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

120. First, Figure 1 of the '338 patent (as reproduced below) is presented as depicting an "exemplary dosing regimen" of the claimed method where "a single 'initial dose' . . . is administered at the beginning of the treatment regimen (i.e. at

'week 0'), two 'secondary doses' are administered at weeks 4 and 8, respectively, and at least six 'tertiary doses' are administered once every 8 weeks."




(Ex.1001, '338 patent, Fig.1, 2:54-60).

121. Based upon my reading of the patent specification, including Figure 1, and the claims of the '338 patent, it is my opinion that Figure 1 represents a dosing regimen that falls squarely within the scope of the challenged claims, including claim 1. For example, the '338 patent states that "FIG. 1 shows an exemplary dosing regimen of the present invention." In addition, the '338 patent explains that the figure illustrates a dosing regimen in which "a single 'initial dose' of VEGF antagonist ('VEGFT') is administered at the beginning of the treatment regimen (i.e. at 'week 0'), two 'secondary doses' are administered at weeks 4 and 8, respectively, and at least six 'tertiary doses' are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc." Because I will be using a modified version of

Figure 1 of the '338 patent below to illustrate how the prior art discloses the claimed dosing regimen, I have prepared a side-by-side table showing how the claimed dosing regimens of the '338 patent correspond to Figure 1 of the '338 patent.

| **Figure 1** | **Claim 1[16]** |
|---|---|
| "a single 'initial dose' of VEGF antagonist ('VEGFT') is administered at the beginning of the treatment regimen (i.e. at 'week 0')" (Ex.1001, '338 patent, 2:55-57). | "a single initial dose of a VEGF antagonist" |
| "two 'secondary doses' are administered at weeks 4 and 8, respectively" (*Id.*, 2:57-58). | "followed by one or more secondary doses of the VEGF antagonist . . . wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose" |
| "and at least six 'tertiary doses' are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc." (*Id.*, 2:58-60). | "followed by one or more tertiary doses of the VEGF antagonist . . . wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose" |

122. In addition, I note that dependent claims 3 and 4 offer a narrower version of claim 1, and further specify *exactly* the regimen depicted in Figure 1. For example, claim 3 specifies "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the

[16] Because the dosing regimen aspects of claim 14 are identical, this analysis would apply equally to that claim.

immediately preceding dose." Compare to the Figure 1 legend: "two 'secondary doses' are administered at weeks 4 and 8, respectively." (*Id.*, 2:57-58).

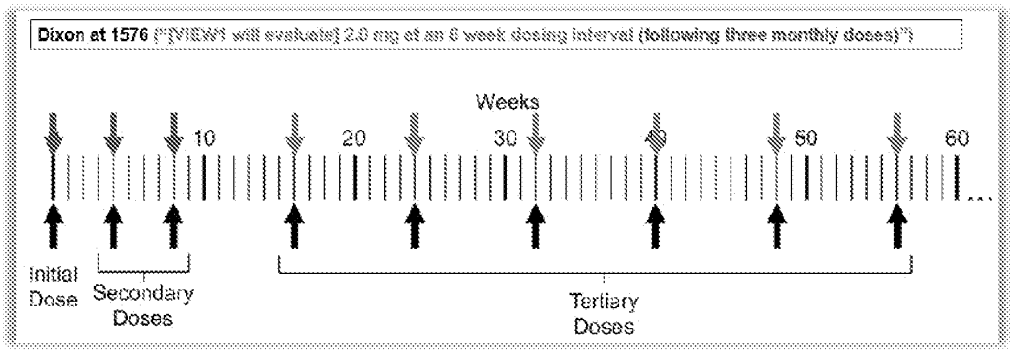
123. Claim 4 is dependent on claim 3, and thus, I have been informed, incorporates all aspects of claim 3, and thus contains the secondary dose information claimed in claim 3. It also specifies that "each tertiary dose is administered 8 weeks after the immediately preceding dose." Compare to the Figure 1 legend: "'tertiary doses' are administered once every 8 weeks thereafter, i.e., at weeks 16, 24, 32, 40, 48, 56, etc." (*Id.*, 2:59-60).

124. Therefore, in my opinion, claim 4 represents the narrowest of the dosing regimen claims, and also corresponds precisely to the dosing regimen portrayed in Figure 1 of the '338 patent, and reproduced above.

125. Because the Figure 1 dosing regimen corresponds to the narrowest dosing regimen claim, it also is representative of claim 1, from which claim 4 depends, as well as each of the other challenged claims directed to dosing regimens (i.e., claims 1, 3, 4, 5, 14, 16, 17, 19). I also note that this regimen comes straight from the VIEW1/VIEW2 Phase 3 studies.

126. To illustrate why Dixon anticipates the challenged claims, I have prepared the following *modified* version of Figure 1 from the '338 patent (set forth below), to show how Dixon discloses the exact dosing regimen set forth in Figure 1

of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent:




(Ex.1001, '338 patent, Fig.1 (modifications added)). Dixon's disclosure of "2.0 mg at an 8 week dosing interval (following three monthly doses)" aligns precisely with Figure 1. For example, Dixon's disclosure of "three monthly doses" (blue arrows), equates to an "initial dose" and two "secondary doses," as those terms are used and defined in the patent. Dixon's disclosure of "an 8 week dosing interval" (red arrows) equates to the claimed "tertiary doses." Dixon further states that "[a]fter the first year of the study, patients will enter a second year of p.r.n. [i.e., as needed] dosing evaluation." (Ex.1006, Dixon, 1576).

127. The last element of claim 1—"wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component

comprising amino acids 232-457 of SEQ ID NO:2"—is merely a recitation of the molecular architecture or structure of the "aflibercept" / "VEGF Trap-Eye" disclosed in Dixon, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093). As a result, through Dixon's disclosure of VEGF Trap-Eye/aflibercept, Dixon discloses this aspect of claim 1.

**1. Claim 1 of the '338 patent is anticipated by Dixon.**

128. Below, I have constructed a chart for the purpose of showing where each and every claim element from claim 1 is found in the Dixon reference:

| Claim 1: | Dixon |
|---|---|
| A method for treating[17] an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a | "Phase III trial of VEGF Trap-Eye" in patients "with neovascular AMD" where VEGF Trap-Eye is administered at "2.0 mg at an 8 week dosing interval |

[17] In my opinion, claim 1 does not specify a particular level of treating, in terms of efficacy measures, and I have been informed that claim preambles are presumed to be non-limiting. However, even if the preamble were a limitation, in my experience, any patient involved in a clinical study is, by definition, being treated. Further, the VEGF Trap-Eye Phase 2 data showed effective treatment of AMD, an angiogenic eye disorder, with a regimen that involved even fewer doses, on average, than the VEGF Trap-Eye Phase 3 dosing regimen would require, which is a regimen that falls squarely within the scope of claim 1 of the '338 patent. The Phase 2 results were publicly available well before the filing date of the '338 patent. (*See, e.g.*, Ex.1006, Dixon, 1576; Ex.1007, Adis, 267-68; Ex.1013, Regeneron (8-May-2008), 1-2; Ex.1056, Regeneron (28-September-2008), 1-2). In addition, the VIEW Phase 3 results using the every-8-week dosing regimen confirm that those prior art regimens treated patients with AMD, and that effective treatment of that patient population is an inherent aspect of those regimens. (Ex.1018, Heier-2012, 2541-45). The same would apply if Regeneron were to argue, as I understand they have in another matter, that the term "tertiary dose" carries with it an efficacy requirement.

| Claim 1: | Dixon |
|---|---|
| VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; | (following three monthly doses)." (Ex.1006, Dixon, 1576). AMD is well known to be an angiogenic eye disorder, and the dosing sequence disclosed for the VIEW1/VIEW2 trials would have involved sequential administration. |
| wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and | "2.0 mg at an 8 week dosing interval (*following three monthly doses*)." (*Id.* (emphasis added)). As I explain above, "three monthly doses" involves a dose at baseline, i.e., day 0, as well as a "secondary dose" one month later (i.e., "4 weeks after the immediately preceding dose"), and another "secondary dose" one month after that (i.e., "4 weeks after the immediately preceding dose"). |
| wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose; | "2.0 mg *at an 8 week dosing interval* (following three monthly doses)." (*Id.* (emphasis added)). As I explain above, an "8 week dosing interval" involves a regimen in which each dose "is administered at least 8 weeks after the immediately preceding dose." |
| wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2. | "One promising new drug is aflibercept (VEGF Trap-Eye) . . . ." (*Id.*, 1573). "VEGF Trap-Eye is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment . . . . VEGF Trap-Eye and aflibercept . . . have the |

| Claim 1: | Dixon |
|---|---|
| | same molecular structure . . . ." (*Id.*, 1575).[18] |

As a result, Dixon anticipates claim 1 of the '338 patent.

**2. Dependent claims 3 and 4 are anticipated by Dixon.**

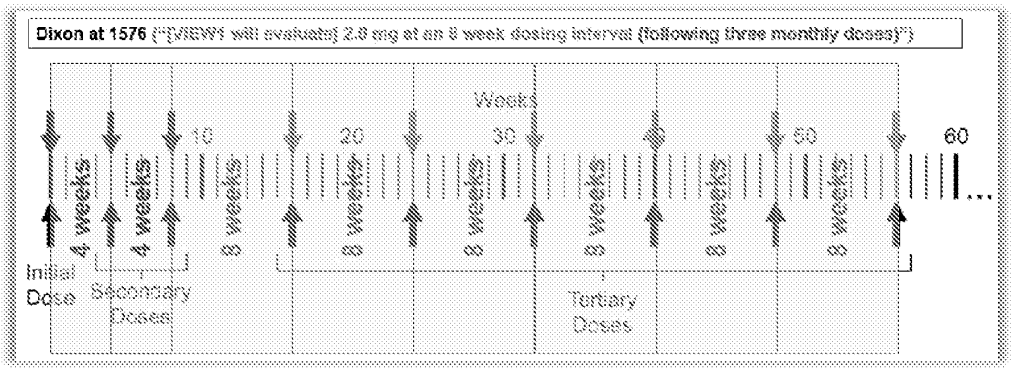
129. I have been informed that claims 3 and 4 can be described as "dependent" on claim 1. It is my understanding that a dependent claim incorporates the elements of the claims from which it depends.

130. Claim 3 limits the method of claim 1 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." And, claim 4 further limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

131. As illustrated in my modified Figure 1 of the '338 patent as provided below, which exemplifies a regimen falling within the scope of all the challenged claims, Dixon discloses the elements of claim 3 (each secondary dose is

[18] As discussed above, the structure and sequence of VEGF Trap-Eye/aflibercept was well known to those of ordinary skill in the art. (*See, e.g.*, *supra* Sec. VIII(A)).

administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose):




(Ex.1001, '338 patent, Fig.1 (modifications added)).

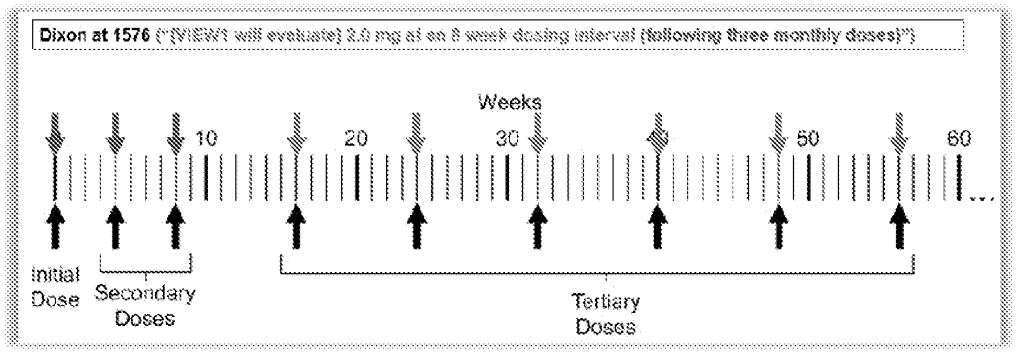
132. Accordingly, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claims 3 and 4 of the '338 patent are anticipated by Dixon.

### 3. Dependent claim 5 is anticipated by Dixon.

133. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

134. Dixon discloses that the every-8-week aspect of the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing [T]he primary

outcome will be the proportion of patients who maintain vision *at week 52*." (emphasis added)). As illustrated in my modified Figure 1 below, the "8 week dosing interval" disclosed in Dixon would result in "at least 5 tertiary doses," e.g., administered at weeks 16, 24, 32, 40, and 48 (red arrows), each administered 8 weeks after the immediately preceding dose:




(Ex.1001, '338 patent, Fig.1 (modifications added)).

135. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 of the '338 patent is anticipated by Dixon.

**4. Dependent claims 6 and 7 are anticipated by Dixon.**

136. Claim 6 is dependent on claim 1 and recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

137. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the treatment of AMD, which is an angiogenic eye disorder. Likewise, the bulk of the reference discusses VEGF Trap-Eye as it relates to the treatment of AMD, including the discussion of the Phase 1 CLEAR-IT-1 clinical trial in patients with neovascular AMD; the Phase 2 CLEAR-IT-2 clinical trials in wet AMD; and the Phase 3 VIEW1 and VIEW2 clinical trials. It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD that the dosing regimen of 3 monthly doses followed by every 8 week dosing was disclosed, after reporting that the Phase 2 trial results had shown mean improvements in visual acuity and retinal thickness, which are key indicators of success when treating AMD. Thus, Dixon discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

138. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 of the '338 patent are anticipated by Dixon.

**5. Dependent claims 8-10 are anticipated by Dixon.**

139. Dependent claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

140. Claim 9 depends from claim 8 and specifies intraocular administration.

141. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

142. Dixon discloses that the VIEW1 and VIEW2 studies "will evaluate the safety and efficacy of ***intravitreal*** VEGF Trap-Eye." (Ex.1006, Dixon, 1576 (emphasis added)). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye. This element is therefore expressly disclosed and taught by Dixon.

143. Therefore, for these reasons, as well as the reasons set forth for claim 1 above, it is my opinion that claims 8-10 are anticipated by Dixon.

**6. Dependent claims 11 and 13 are anticipated by Dixon.**

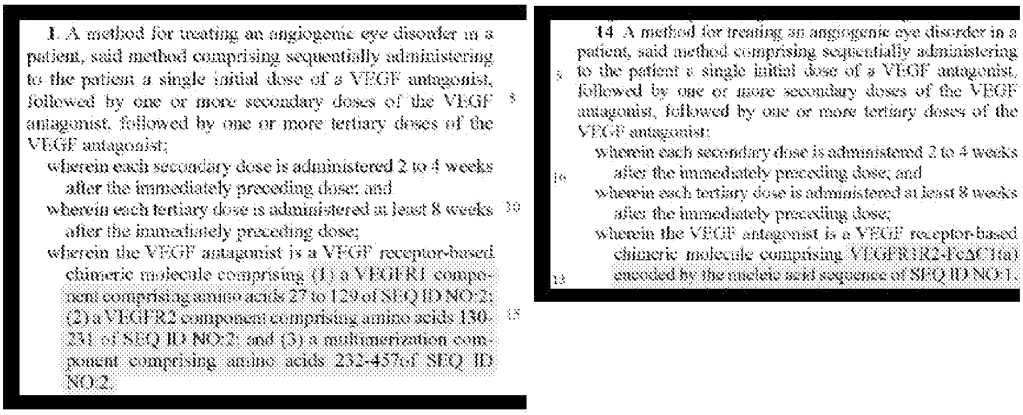
144. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

145. Dixon discloses the treatment arms in the VIEW1 and VIEW2 studies which included "intravitreal VEGF Trap-Eye at…2.0 mg at an 8 week dosing interval (following three monthly doses)." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses the doses of claims 11 and 13.

146. Therefore, for these reasons, as well as the reasons set forth above for claim 10 and claim 1, it is my opinion that claims 11 and 13 are anticipated by Dixon.

### 7. Independent claim 14 is anticipated by Dixon.

147. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause:



1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2.

14. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist:

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-Fc$\Delta$C1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

148. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶ 128), it is also my opinion that Dixon discloses these identical elements in claim 14.

149. Second, in my opinion, Dixon also discloses the VEGF antagonist element of claim 14. Just as for claim 1, Dixon expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-

C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain); *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

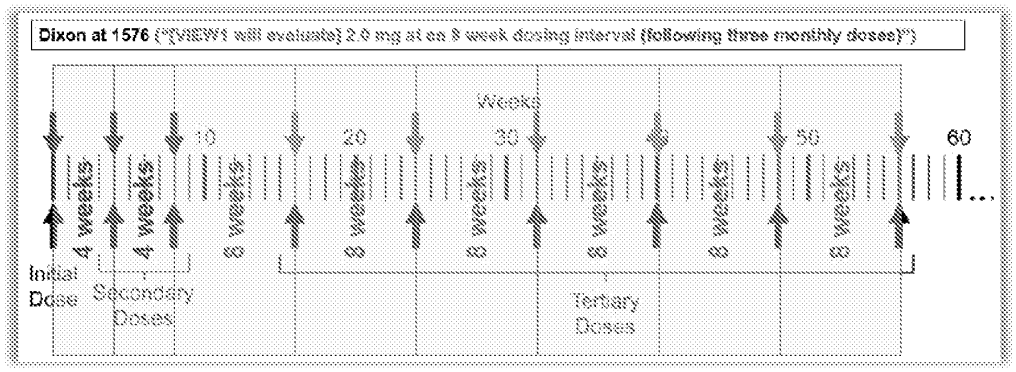
150. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Dixon.

**8. Dependent claims 16 and 17 are anticipated by Dixon.**

151. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

152. As I explained with respect to claims 3 and 4 above, Dixon discloses the elements of claim 16 (each secondary dose administered 4 weeks after the

immediately preceding dose) and claim 17 (each tertiary dose is administered 8 weeks after the immediately preceding dose), as is illustrated in modified Figure 1 below:




(Ex.1001, '338 patent, Fig.1 (modifications added)).

153. Accordingly, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claims 16 and 17 of the '338 patent are anticipated by Dixon.

**9. Dependent claims 18 and 20 are anticipated by Dixon.**

154. Claim 18 is dependent on claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 is dependent on claim 14 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

155. The Dixon reference indicates in the title that VEGF Trap-Eye was being studied for the treatment of AMD. Likewise, the bulk of the reference discusses VEGF Trap-Eye as it relates to the treatment of AMD, including the discussion of the Phase 1 CLEAR-IT-1 clinical trial in patients with neovascular AMD; the Phase 2 CLEAR-IT-2 clinical trials in wet AMD; and the Phase 3 VIEW1 and VIEW2 clinical trials. It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD that the dosing regimen of 3 monthly doses followed by every 8 week dosing was disclosed, after reporting that the Phase 2 trial results had shown mean improvements in visual acuity and retinal thickness, which are key indicators of success when treating AMD. Dixon therefore expressly discloses treating an angiogenic eye disorder, including AMD, as required by claims 18 and 20.

156. Thus, for these reasons, as well as for the reasons discussed above for claims 14, 16, and 17, it is my opinion that claims 18 and 20 of the '338 patent are anticipated by Dixon.

**10. Dependent claim 19 is anticipated by Dixon.**

157. Claim 19 claims the method of claim 14, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

158. Dixon discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing . . . . [T]he primary outcome will be the proportion of patients who maintain vision *at week 52*." (emphasis added)).

159. As explained above with respect to claim 5, moreover, one year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses (red arrows in above figure). For example, after three monthly doses at weeks 0, 4, and 8, the every-8-week dosing regimen disclosed in Dixon for the VIEW1 and VIEW2 studies would result in doses being administered at weeks 16, 24, 32, 40, and 48, meaning that "at least 5 tertiary doses" would be administered at least 8 weeks after the immediately preceding dose, before the end of the one year trial.

160. Thus, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claim 19 of the '338 patent is anticipated by Dixon.

**11. Dependent claims 21-23 are anticipated by Dixon.**

161. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

162. Claim 22 depends from claim 21 and specifies intraocular administration.

163. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

164. To a person of ordinary skill in the art, it is well understood that intravitreal administration is a form of intraocular administration. Intraocular administration refers to administration to the eye generally, while intravitreal administration, a subset of intraocular administration, refers to administration directly into the vitreous of the eye.

165. In Dixon's disclosure of the VIEW1 and VIEW2 studies, Dixon stated that the study "will evaluate the safety and efficacy of intravitreal VEGF Trap-Eye." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses intravitreal administration.

166. Therefore, for these reasons, as well as for the reasons discussed above for claim 14, it is my opinion that claims 21-23 are anticipated by Dixon.

**12. Dependent claims 24 and 26 are anticipated by Dixon.**

167. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

168. Dixon discloses the VIEW1 and VIEW2 studies in which the treatment arms included "intravitreal VEGF Trap-Eye at . . . 2.0 mg at an 8 week dosing

interval (following three monthly doses)." (Ex.1006, Dixon, 1576). Dixon therefore expressly discloses the doses of claims 24 and 26.

169. Therefore, for these reasons, as well as the reasons set forth above for the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Dixon.

### B. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by Adis (Ex.1007).

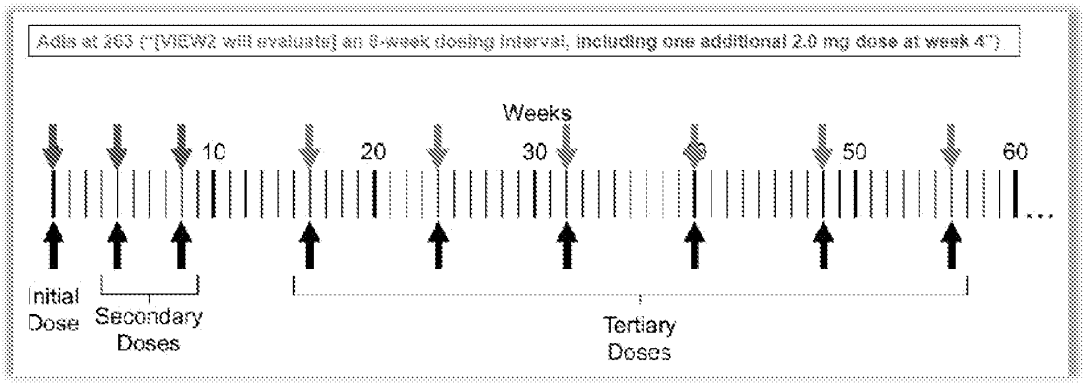
#### 1. Claim 1 of the '338 patent is anticipated by Adis.

170. Claim 1 of the '338 patent has been set forth above.

171. I was asked to review the challenged claims of the '338 patent and compare them to the disclosures of Adis. It is my opinion that Adis discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

172. For example, like Dixon above, Adis discloses Regeneron's planned Phase 3 trials being conducted with VEGF Trap-Eye, VIEW1 and VIEW2. Adis discloses the VIEW regimen, i.e., "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4." (Ex.1007, Adis, 263). In other words, one of the dosing regimens being tested in the VIEW trials was every-8-week dosing following three monthly doses. This has been shown using the same overlay presented above, in which I have used Figure 1 of the '338 patent, which shows a

regimen that exemplifies each challenged claim, to illustrate how Adis discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:




(Ex.1001, '338 patent, Fig.1 (modifications added)).

173. While Adis does not use the exact terms "initial," "secondary," and "tertiary," one of ordinary skill in the art readily would have recognized that the "initial dose" would have been the first dose given—in this case the dose given at time zero—and that the "secondary doses . . . wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose," could be found in Adis' disclosure of "an 8-week dosing interval, *including one additional 2.0 mg dose at week 4*" (blue arrows). (*See, e.g.*, Ex.1007, Adis, 263 (emphasis added)).

174. Similarly, one of ordinary skill in the art would have recognized that the "tertiary doses . . . wherein each tertiary dose is administered at least 8 weeks

after the immediately preceding dose," correspond to the "8-week dosing interval" doses disclosed in Adis (red arrows). (*See, e.g., id.*).

175. In my opinion, the VIEW dosing regimen described in Adis is the precise dosing regimen that was described in Figure 1 in the '338 patent and which falls squarely within the scope of claim 1.

176. With respect to the VEGF antagonist element of claim 1, I note that this description is merely a recitation of the molecular architecture of the "aflibercept" and "VEGF Trap-Eye" disclosed in Adis, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain); *id.*, 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the

same drug); Ex.1093). As a result, through Adis' disclosure of VEGF Trap-Eye/aflibercept, Adis discloses this aspect of claim 1.[19]

177. Accordingly, for these reasons, it is my opinion that claim 1 of the '338 patent is anticipated by Adis.

**2. Dependent claims 3 and 4 are anticipated by Adis.**

178. Dependent claim 3 claims the method of claim 1, "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

179. Claim 4 claims the method of claim 3, "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

180. As discussed above and illustrated in my modified Figure 1 of the '338 patent, Adis discloses the elements of claim 3 (each secondary dose administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose):

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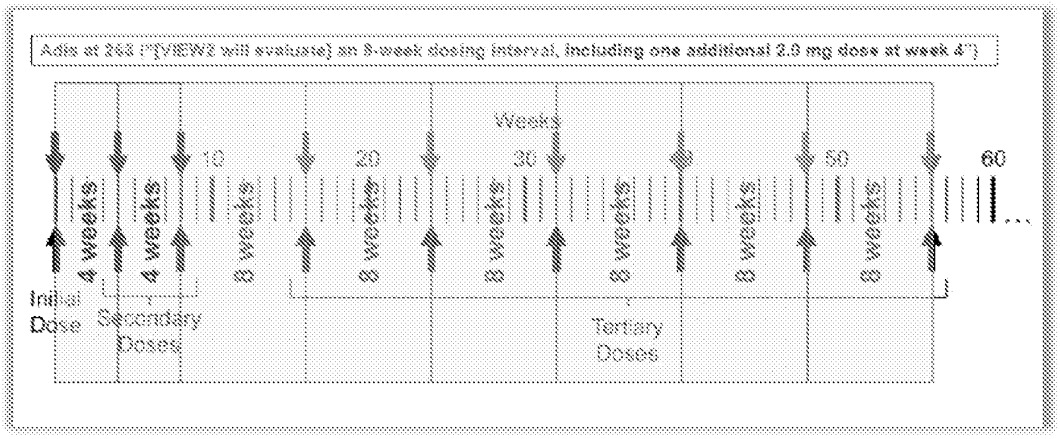
[19] Regarding the preamble, *see, e.g.*, *supra* note 18; Ex.1007, Adis, 268 ("After the last fixed-dose administration at week 12, patients from all dose groups required on average only one additional injection over the following 20 weeks to maintain visual acuity gain achieved.").




(Ex.1001, '338 patent, Fig.1 (modifications added)).

181. Accordingly, for these reasons, as well as the reasons presented for claim 1, it is my opinion that claims 3 and 4 of the '338 patent are anticipated by Adis.

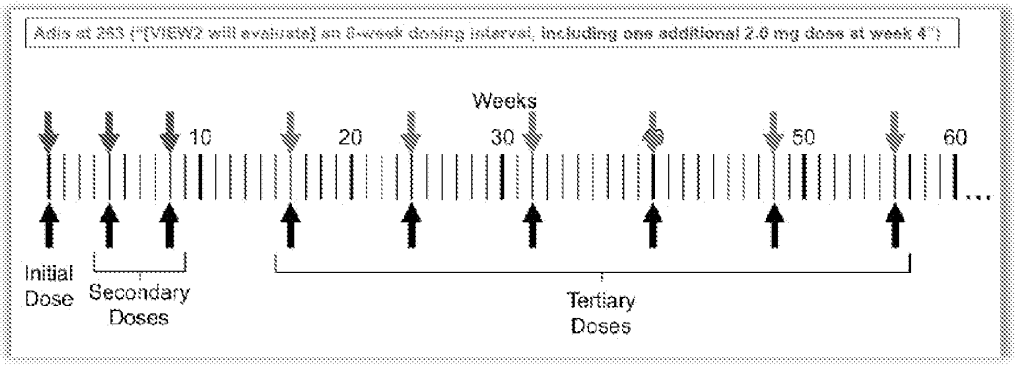
### 3. Dependent claim 5 is anticipated by Adis.

182. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

183. Adis discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (Ex.1007, Adis, 263 ("Patients will continue to be treated and followed for an additional year, ***after the first year of treatment***" and "[t]he primary endpoint

will be the proportion of patients treated with aflibercept who maintain vision ***at the end of 1 year*** compared with ranibizumab patients." (emphases added)).

184. One year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses administered at least 8 weeks after the immediately preceding dose. Again, a graphic is useful in illustrating this:




(Ex.1001, '338 patent, Fig.1 (modifications added)). Using the modified graphic from the '338 patent, it is apparent that the every-8-week dosing regimen disclosed in Adis for the VIEW1 and VIEW2 studies would result in "tertiary" doses being administered at least at weeks 16, 24, 32, 40, and 48, meaning that "at least 5 tertiary doses" would be administered before the end of the one-year trial.

185. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 of the '338 patent is anticipated by Adis.

### 4. Dependent claims 6 and 7 are anticipated by Adis.

186. Claim 6 is dependent on claim 1 and recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

187. The Adis reference indicates in the abstract that aflibercept was being developed for eye disorders and that "[b]lockade of VEGF can also prevent blood vessel formation and vasuclar [sic] leakage associated with wet age-related macular degeneration (AMD)." (Ex.1007, Adis, 261). Likewise, Adis discusses Regeneron's disclosures of the VIEW1 and VIEW2 trials, which were intended to study VEGF Trap-Eye/aflibercept in wet AMD. (*Id.*, 263). It is in the discussion of the VIEW1 and VIEW2 trials for wet AMD, which is an angiogenic eye disorder, that the dosing regimen of doses at weeks 0, 4, and 8, followed by every-8-week dosing, was disclosed. Thus, Adis discloses the treatment of AMD, a well-known angiogenic eye disorder.

188. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 of the '338 patent are anticipated by Adis.

### 5. Dependent claims 8-10 are anticipated by Adis.

189. Dependent claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

190. Claim 9 depends from claim 8 and specifies intraocular administration.

191. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

192. In Adis' disclosure of the VIEW studies, Adis states that the study "will evaluate the safety and efficacy of intravitreal aflibercept." (Ex.1007, Adis, 263). Adis also notes that Regeneron's Phase 2 trial was designed to "evaluate the safety and efficacy of intravitreal aflibercept using different doses and dose regimens." (*Id.*). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye. This element is therefore expressly disclosed and taught by Adis.

193. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 of the '338 patent are anticipated by Adis.

### 6. Dependent claims 11 and 13 are anticipated by Adis.

194. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the

VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

195. Adis discloses the VIEW1 and VIEW2 studies in which the treatment arms included VEGF Trap-Eye/aflibercept administered at a 2.0 mg dose. (Ex.1007, Adis, 263). Adis therefore expressly discloses the doses of claims 11 and 13.

196. Therefore, for these reasons, as well as the reasons set forth above for claim 10 and claim 1, it is my opinion that claims 11 and 13 are anticipated by Adis.

**7. Independent claim 14 is anticipated by Adis.**

197. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

198. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 170-77), it is also my opinion that Adis discloses these identical elements in claim 14.

199. Second, in my opinion, Adis discloses the VEGF antagonist element of claim 14. Adis expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide

sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

200. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Adis.

**8. Dependent claims 16 and 17 are anticipated by Adis.**

201. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

202. These elements are similar in scope to those discussed above with respect to claims 3 and 4, and as I explained with respect to those claims, Adis

discloses the elements of "each secondary dose is administered 4 weeks after the immediately preceding dose" and "each tertiary dose is administered 8 weeks after the immediately preceding dose." (*See, e.g.*, Ex.1007, Adis, 263 ("2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week 4.")).

203. Accordingly, for these reasons, as well as for the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 of the '338 patent are anticipated by Adis.

**9. Dependent claims 18 and 20 are anticipated by Adis.**

204. Claim 18 depends from claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 depends from claim 14 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

205. These elements are similar in scope to those discussed above with respect to claims 6 and 7, and as I explained with respect to those claims, Adis discloses the VIEW1 and VIEW2 trials, and the treatment arms used therein, which were designed to assess wet AMD. (*See, e.g.*, Ex.1007, Adis, 263 ("Regeneron and Bayer initiated a phase III trial of aflibercept in approximately 1200 patients with the neovascular form of wet AMD . . . .")). Adis therefore expressly discloses treating AMD, an angiogenic eye disorder.

206. Thus, for these reasons, as well as for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 of the '338 patent are anticipated by Adis.

**10. Dependent claim 19 is anticipated by Adis.**

207. Claim 19 claims the method of claim 14, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

208. As explained above with respect to claim 5, Adis discloses that the VIEW1 and VIEW2 clinical trials will last at least a year. (*See, e.g.*, Ex.1007, Adis, 263 ("The primary endpoint will be the proportion of patients treated with aflibercept who maintain vision *at the end of 1 year* . . . .") (emphasis added)). One year of dosing on an every-8-week dosing schedule after three monthly doses would result in at least 5 "tertiary" doses administered at least 8 weeks after the immediately preceding dose.

209. Thus, for these reasons, as well as for the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 of the '338 patent is anticipated by Adis.

### 11. Dependent claims 21-23 are anticipated by Adis.

210. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

211. Claim 22 depends from claim 21 and specifies intraocular administration.

212. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

213. As discussed above with respect to claims 8-10, Adis discloses that the VIEW trials, and the treatment arms used therein, were assessing intravitreally-administered aflibercept. (*See, e.g.*, Ex.1007, Adis, 263 ("VIEW1 . . . will evaluate the safety and efficacy of intravitreal aflibercept . . . .")). Adis therefore expressly discloses intravitreal administration of the VEGF antagonist.

214. Therefore, for these reasons, as well as for the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by Adis.

### 12. Dependent claims 24 and 26 are anticipated by Adis.

215. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

216. As discussed above with respect to claims 11 and 13, Adis discloses that the VIEW1 and VIEW2 studies were intended to assess a 2.0 mg dose. (*See, e.g.*, Ex.1007, Adis, 263). Adis therefore expressly discloses a 2.0 mg doses of VEGF Trap-Eye/aflibercept.

217. Therefore, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Adis.

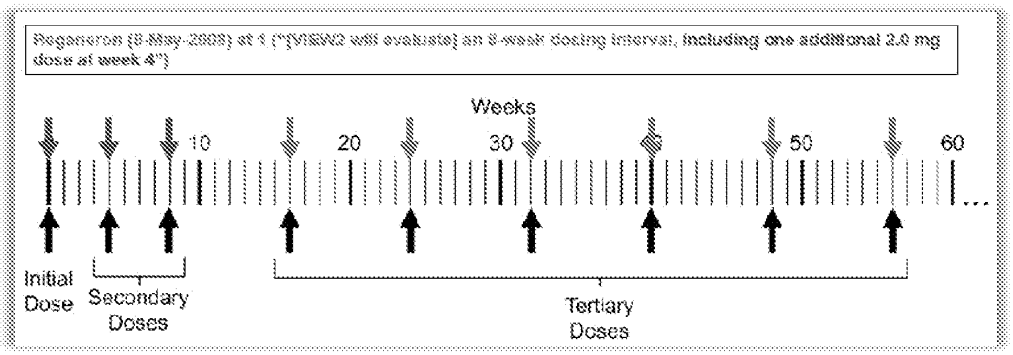
### C. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by the Regeneron Press Release Dated May 8, 2008 (Regeneron (8-May-2008) (Ex.1013).

#### 1. Independent claim 1 of the '338 patent is anticipated by Regeneron (8-May-2008).

218. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of the Regeneron Press Release, dated May 8, 2008. It is my opinion that Regeneron (8-May-2008) discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

219. For example, like Dixon and Adis above, Regeneron (8-May-2008) discloses the VIEW Phase 3 trials being conducted with VEGF Trap-Eye, and explains that VIEW2 will assess VEGF Trap-Eye at "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, Regeneron

(8-May-2008), 1). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how Regeneron (8-May-2008) discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:




(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing "at an 8-week dosing interval" would result in doses at day 0 and at week 8, and when adding "one additional 2.0 mg dose at week 4," this would result in three monthly doses (blue arrows) (i.e., doses at day 0 (i.e. "initial dose") and at weeks 4 and 8 (i.e., "secondary doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (red arrows) (i.e., "tertiary doses")).

220. Regeneron (8-May-2008) further states that "[a]fter the first year of treatment, patients will continue to be followed and treated for another year on a flexible, criteria-based extended regimen with a dose administered at least every 12

weeks, but not more often than every 4 weeks." (Ex.1013, Regeneron (8-May-2008), 1).

221. With respect to the VEGF antagonist element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in Regeneron (8-May-2008), a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2) and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093). As a result, through Regeneron (8-May-2008)'s disclosure

of VEGF Trap-Eye/aflibercept, Regeneron (8-May-2008) discloses this aspect of claim 1. .[20]

222. Accordingly, for at least these reasons, it is my opinion that claim 1 is anticipated by Regeneron (8-May-2008).

**2. Dependent claims 3 and 4 are anticipated by Regeneron (8-May-2008).**

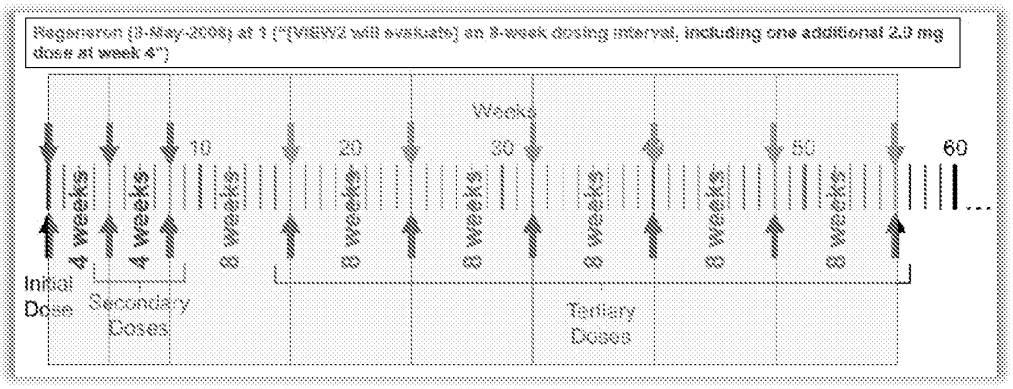
223. Dependent claim 3 claims the method of claim 1, "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

224. Claim 4 claims the method of claim 3, "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

225. As illustrated in my modified Figure 1 of the '338 patent below, Regeneron (8-May-2008) discloses the elements of claims 3 and 4. In discussing the first year of the VIEW2 study, Regeneron (8-May-2008) states patients will be administered "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg

[20] Regarding the preamble, *see, e.g.*, *supra* note 18; Ex.1013, Regeneron (8-May-2008), 1 ("[P]atients on the PRN dosing schedule maintained the gain in visual acuity and decrease in retinal thickness achieved at week 12 through week 32 of the study.").

dose at week four." (Ex.1013, Regeneron (8-May-2008), 1). In my opinion, and consistent with the figure below, this dosing schedule consists of a 2.0 mg dose at day 0 (i.e., an "initial dose"), 2.0 mg doses at weeks 4 and 8 (i.e., "secondary doses"), and 2.0 mg doses every 8 weeks (i.e., "tertiary doses") for the remainder of the year:




(Ex.1001, '338 patent, Fig.1 (modifications added (initial and secondary doses indicated by blue arrows and tertiary doses indicated by red arrows)).

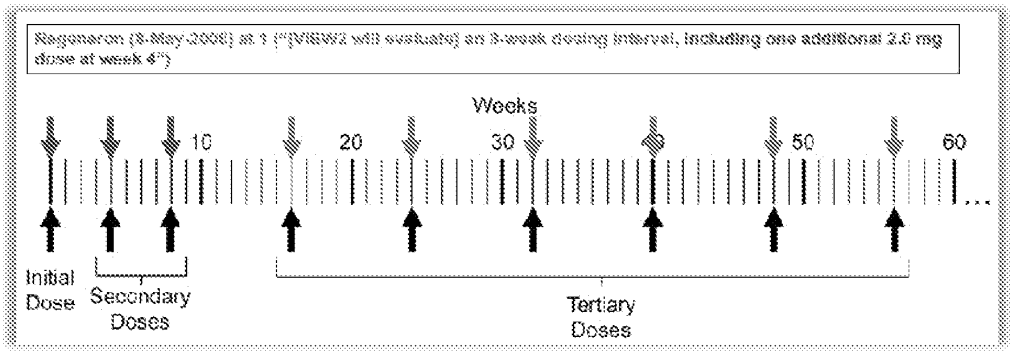
226. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by Regeneron (8-May-2008).

### 3. Dependent claim 5 is anticipated by Regeneron (8-May-2008).

227. For the same reasons as above for claims 3 and 4, Regeneron (8-May-2008) discloses the elements of claim 5. Dependent claim 5 recites "[t]he method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after

the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

228. Regeneron (8-May-2008) discloses that the VIEW2 clinical trial will last at least a year. (Ex.1013, Regeneron (8-May-2008), 1 ("In the ***first year***, the VIEW 2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of . . . 2.0 mg at an 8-week dosing interval . . . ." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (red arrows):




(Ex.1001, '338 patent, Fig.1 (modifications added)).

229. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by Regeneron (8-May-2008).

#### 4. Dependent claims 6 and 7 are anticipated by Regeneron (8-May-2008).

230. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

231. Claim 7 further limits the method of claim 6 to recite "wherein the angiogenic eye disorder is age related macular degeneration."

232. Regeneron (8-May-2008) expressly discloses that VIEW2 is an investigation of efficacy and safety of VEGF Trap-Eye in wet AMD, which is a well-known angiogenic eye disorder. (Ex.1013, Regeneron (8-May-2008), 1; *see also id.*, Title).

233. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by Regeneron (8-May-2008).

#### 5. Dependent claims 8-10 are anticipated by Regeneron (8-May-2008).

234. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

235. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

236. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

237. Regeneron (8-May-2008) discloses that "[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection." (Ex.1013, Regeneron (8-May-2008), 1). This element is therefore expressly disclosed and taught by Regeneron (8-May-2008).

238. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by Regeneron (8-May-2008).

**6. Dependent claims 11 and 13 are anticipated by Regeneron (8-May-2008).**

239. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

240. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

241. Regeneron (8-May-2008) discloses that the "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at" a dose of 2.0 mg. (Ex.1013, Regeneron

(8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses the doses of claims 11 and 13.

242. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1 and the claims from which claims 11 and 13 depend, it is my opinion that claims 11 and 13 are anticipated by Regeneron (8-May-2008).

**7. Independent claim 14 is anticipated by Regeneron (8-May-2008).**

243. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

244. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 218-22), it is also my opinion that Regeneron (8-May-2008) discloses these identical elements in claim 14.

245. Second, in my opinion, Regeneron (8-May-2008) discloses the VEGF antagonist element of claim 14. Just as for claim 1, Regeneron (8-May-2008) expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced

amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

246. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by Regeneron (8-May-2008).

**8. Dependent claims 16 and 17 are anticipated by Regeneron (8-May-2008).**

247. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

248. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

249. As discussed with respect to claims 3 and 4 above, Regeneron (8-May-2008) discloses the elements of claims 16 and 17. Regeneron (8-May-2008) states patients will be administered "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four." (Ex.1013, Regeneron (8-May-2008), 1). In my opinion, this dosing schedule consists of an initial 2.0 mg dose, a first secondary 2.0 mg dose at week 4, a second secondary 2.0 mg dose at week 8, and tertiary 2.0 mg doses every 8 weeks for the remainder of the year.

250. For these reasons, as well as the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 are anticipated by Regeneron (8-May-2008).

**9. Dependent claims 18 and 20 are anticipated by Regeneron (8-May-2008).**

251. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

252. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

253. As discussed with claims 6 and 7 above, Regeneron (8-May-2008) discloses that VIEW2 is an investigation of efficacy and safety of VEGF Trap-Eye

in wet AMD. (Ex.1013, Regeneron (8-May-2008), 1; *see also id.*, Title). Regeneron (8-May-2008) therefore expressly discloses treating AMD, an angiogenic eye disorder.

254. Therefore, for these reasons, as well as for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by Regeneron (8-May-2008).

**10. Dependent claim 19 is anticipated by Regeneron (8-May-2008).**

255. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

256. As discussed with claim 5, Regeneron (8-May-2008) discloses that the VIEW2 clinical trial will last at least a year. (Ex.1013, Regeneron (8-May-2008), 1 ("In the ***first year***, the VIEW 2 . . . study will evaluate the safety and efficacy of VEGF Trap-Eye at doses of . . . 2.0 mg at an 8-week dosing interval . . . ." (emphasis added))). An 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

257. Accordingly, for these reasons, as well as for the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by Regeneron (8-May-2008).

### 11. Dependent claims 21-23 are anticipated by Regeneron (8-May-2008).

258. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

259. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

260. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

261. As discussed with claims 8-10 above, Regeneron (8-May-2008) discloses that "[b]oth VIEW 1 and VIEW 2 are designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection." (Ex.1013, Regeneron (8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses intravitreal administration of the VEGF antagonist.

262. Thus, for these reasons, as well as for the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by Regeneron (8-May-2008).

### 12. Dependent claims 24 and 26 are anticipated by Regeneron (8-May-2008).

263. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

264. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

265. As discussed with claims 11 and 13 above, Regeneron (8-May-2008) discloses that the "VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study will evaluate the safety and efficacy of VEGF Trap-Eye at" a dose of 2.0 mg. (Ex.1013, Regeneron (8-May-2008), 1). Regeneron (8-May-2008) therefore expressly discloses the claimed doses.

266. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by Regeneron (8-May-2008).

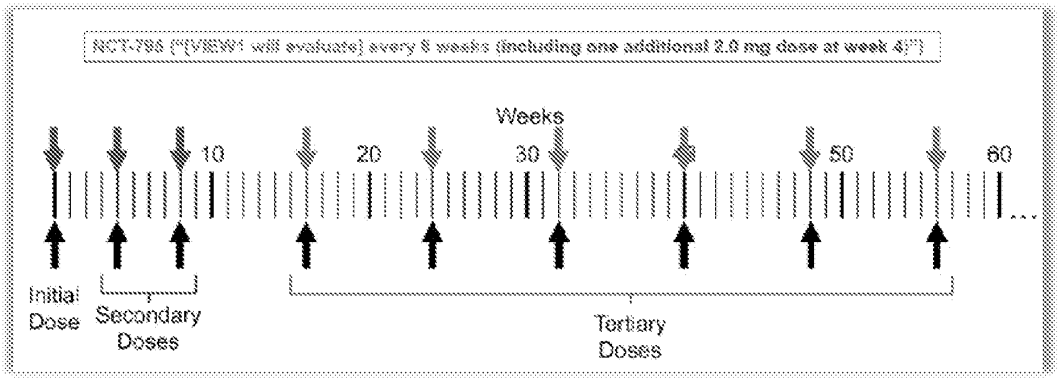
## D. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by NCT00509795 (NCT-795) (Ex.1014).

### 1. Independent claim 1 of the '338 patent is anticipated by NCT-795.

267. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of NCT-795. As with the other references

above that disclose Regeneron's VIEW trials and the dosing regimens used in those trials, it is my opinion that NCT-795 discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

268. For example, NCT-795 describes VIEW1 as a Phase 3 trial being conducted with VEGF Trap-Eye in patients with AMD and including a treatment arm in which 2.0 mg of VEGF Trap-Eye will be "administered every 8 weeks (including one additional 2.0 mg dose at week 4)." (Ex.1014, NCT-795, 8). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how NCT-795 discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:




(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing every eight weeks would result in doses at day 0 and at week 8, and when adding one additional dose at week 4, this would result in three monthly doses (blue arrows)

(i.e., doses at day 0 (i.e., "initial dose") and at weeks 4 and 8 (i.e., "secondary doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (red arrows) (i.e., "tertiary doses")).

269. With respect to the last element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in NCT-795, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093).[21]

[21] Regarding the preamble, *see, e.g.*, *supra* note 18.

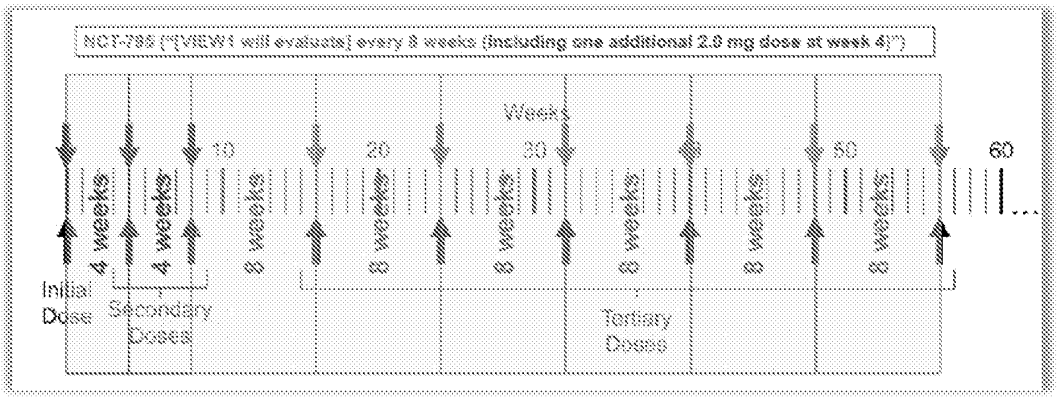
270. Accordingly, for at least these reasons, it is my opinion that claim 1 is anticipated by NCT-795.

**2. Dependent claims 3 and 4 are anticipated by NCT-795.**

271. Dependent claim 3 recites "[t]he method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

272. Claim 4 additionally limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

273. As illustrated in my modified Figure 1 of the '338 patent below, NCT-795 discloses the elements of claims 3 and 4. NCT-795 discloses a treatment arm wherein subjects are to receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (Ex.1014, NCT-795, 8). In my opinion, this dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year:




(Ex.1001, '338 patent, Fig.1 (modifications added)).

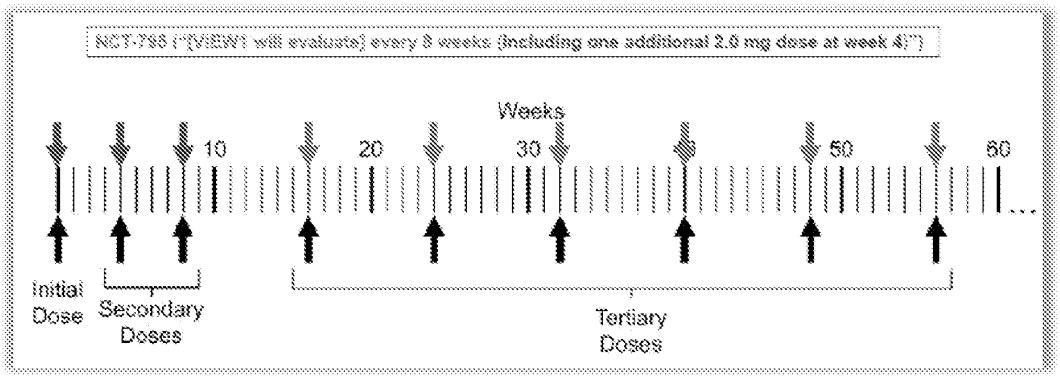
274. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by NCT-795.

### 3. Dependent claim 5 is anticipated by NCT-795.

275. For the same reasons as above for claims 3 and 4, NCT-795 discloses the elements of claims 5. Dependent claim 5 recites "[t]he method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

276. NCT-795 discloses the clinical study will last at least a year. (Ex.1014, NCT-795, 8 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) ***during the first year***." (emphasis added))). As

illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (red arrows):




(Ex.1001, '338 patent, Fig.1 (modifications added)).

277. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by NCT-795.

**4. Dependent claims 6 and 7 are anticipated by NCT-795.**

278. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

279. Claim 7 further limits the method of claim 6 to "wherein the angiogenic eye disorder is age related macular degeneration."

280. NCT-795 discloses that the title of the Phase 3 clinical study is "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration." (Ex.1014, NCT-795, 3). Thus, NCT-795 expressly discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

281. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by NCT-795.

**5. Dependent claims 8-10 are anticipated by NCT-795.**

282. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

283. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

284. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

285. NCT-795 discloses that the Phase 3 study will test repeated doses of intravitreal VEGF Trap in subjects with AMD." (Ex.1014, NCT-795, 3). NCT-795 therefore expressly discloses intravitreal administration.

286. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by NCT-795.

**6. Dependent claims 11 and 13 are anticipated by NCT-795.**

287. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

288. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

289. NCT-795 discloses Phase 3 treatment arms using 2.0 mg of VEGF Trap-Eye. (Ex.1014, NCT-795, 6-8). NCT-795 therefore expressly discloses doses of claims 11 and 13.

290. Accordingly, for these reasons, as well as for the reasons discussed above for claims 1 and 8-10, it is my opinion that claims 11 and 13 are anticipated by NCT-795.

**7. Independent claim 14 is anticipated by NCT-795.**

291. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

292. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 267-70), it is also my opinion that NCT-795 discloses these identical elements in claim 14.

293. Second, in my opinion, NCT-795 discloses the VEGF antagonist element of claim 14. Just as for claim 1, NCT-795 expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a).")); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094). .

294. Therefore, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by NCT-795.

**8. Dependent claims 16 and 17 are anticipated by NCT-795.**

295. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

296. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

297. As discussed with respect to claims 3 and 4 above, NCT-795 discloses the elements of claims 16 and 17. (Ex.1014, NCT-795, 8). In my opinion, it was well established that the VIEW1 dosing schedule consists of an initial 2.0 mg dose, a first secondary 2.0 mg dose at week 4, a second secondary 2.0 mg dose at week 8, and tertiary 2.0 mg doses every 8 weeks for the remainder of the year.

298. Therefore, for these reasons, as well as the reasons discussed above for claims 3, 4, and 14, it is my opinion that claims 16 and 17 are anticipated by NCT-795.

**9. Dependent claims 18 and 20 are anticipated by NCT-795.**

299. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

300. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

301. As discussed with claims 6 and 7 above, NCT-795 discloses the title of the VIEW1 clinical study as "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration." (Ex.1014, NCT-795, 3). NCT-795 therefore expressly discloses treating AMD, an angiogenic eye disorder.

302. Therefore, for these reasons, as well as the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by NCT-795.

**10. Dependent claim 19 is anticipated by NCT-795.**

303. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

304. As discussed with claim 5, NCT-795 discloses that the VIEW1 clinical study will last at least a year. (Ex.1014, NCT-795, 8 ("2.0 mg VEGF Trap-Eye

administered every 8 weeks (including one additional 2.0 mg dose at week 4) ***during the first year***." (emphasis added))). As illustrated above in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses called for in the VIEW1 trial, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

305. Accordingly, for these reasons, as well as the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by NCT-795.

**11. Dependent claims 21-23 are anticipated by NCT-795.**

306. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

307. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

308. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

309. As discussed with claims 8-10 above, NCT-795 discloses that the VIEW1 Phase 3 study will test repeated doses of intravitreal VEGF Trap in subjects with AMD. (Ex.1014, NCT-795, 3). NCT-795 therefore discloses intravitreal administration of VEGF Trap-Eye/aflibercept.

310. Thus, for these reasons, as well as the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by NCT-795.

**12. Dependent claims 24 and 26 are anticipated by NCT-795.**

311. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

312. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

313. As discussed with claims 11 and 13 above, NCT-795 discloses VIEW1 Phase 3 treatment arms using 2.0 mg of VEGF Trap-Eye. (Ex.1014, NCT-795, 6-8). NCT-795 therefore expressly discloses the claimed doses.

314. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by NCT-795.

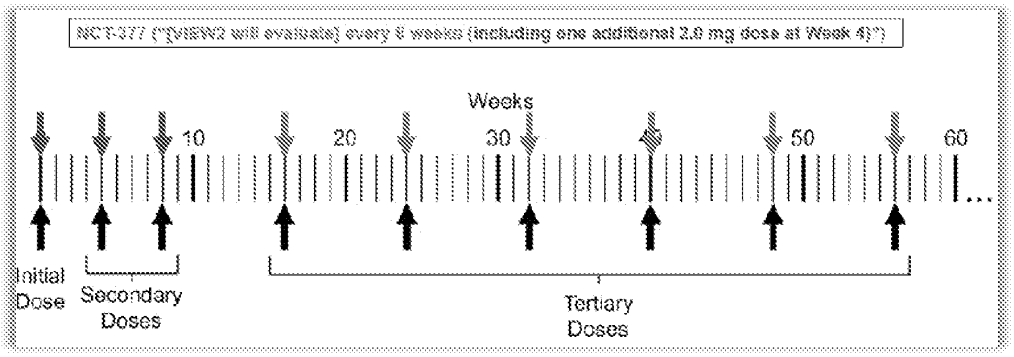
**E. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Anticipated by NCT00637377 (NCT-377) (Ex.1015).**

**1. Independent claim 1 of the '338 patent is anticipated by NCT-377.**

315. I have been asked to review the challenged claims of the '338 patent and compare them to the disclosures of NCT-377. As with the other references above that disclose Regeneron's VIEW trials and the dosing regimens used in those

trials, it is my opinion that NCT-377 discloses every element of the claimed method(s) and thus anticipates each of the challenged claims of the '338 patent.

316. For example, NCT-377 discloses the VIEW2 Phase 3 trial being conducted with VEGF Trap-Eye in patients with AMD and including a treatment arm in which 2.0 mg of VEGF Trap-Eye will be "administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 5-6). This has been illustrated using the same overlay presented above, in which I have used Figure 1 of the '338 patent to illustrate how NCT-377 discloses the exact dosing regimen set forth in Figure 1 of the '338 patent, as well as that which is claimed in the challenged claims of the '338 patent, as depicted here:




(Ex.1001, '338 patent, Fig.1 (modifications added)). In other words, dosing every eight weeks would result in doses at day 0 and at week 8, and when adding one additional dose at week 4, this would result in three monthly doses (blue arrows) (i.e., doses at day 0 (i.e., "initial dose") and at weeks 4 and 8 (i.e., "secondary

doses")). Thereafter, an eight-week dosing interval will result in injections at weeks 16, 24, 32, 40, and 48 (red arrows) (i.e., "tertiary doses")).

317. NCT-377 further states that subjects will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks." (Ex.1015, NCT-377, 6).

318. With respect to the last element of claim 1, as I discuss above, it is merely a recitation of the molecular architecture of the "VEGF Trap-Eye" disclosed in NCT-377, a fact that was disclosed well before January 2011. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and

VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1093).[22]

319. For at least these reasons, it is my opinion that claim 1 is anticipated by NCT-377.

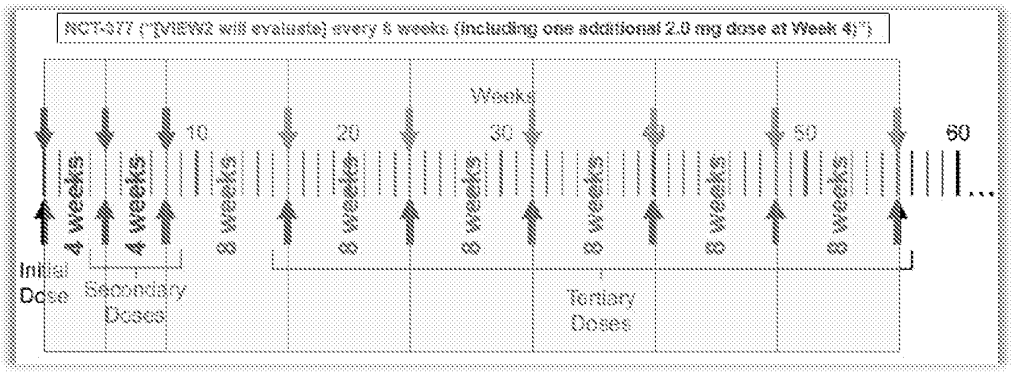
**2. Dependent claims 3 and 4 are anticipated by NCT-377.**

320. Claim 3 recites "[t]he method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

321. Claim 4 additionally limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

322. As illustrated in my modified Figure 1 of the '338 patent below, NCT-377 discloses the elements of claims 3 and 4. NCT-377 states that subjects in one of the four treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). In my opinion, this dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year:

[22] Regarding the preamble, *see, e.g.*, *supra* note 18.




(Ex.1001, '338 patent, Fig.1 (modifications added)).

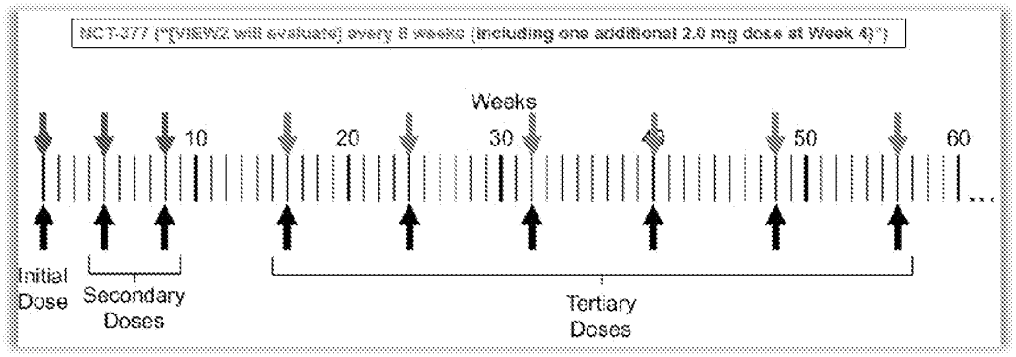
323. Thus, for these reasons, as well as the reasons discussed above for claim 1, it is my opinion that claims 3 and 4 are anticipated by NCT-377.

### 3. Dependent claim 5 is anticipated by NCT-377.

324. For the same reasons as above for claims 3 and 4, NCT-377 discloses the elements of claim 5. Dependent claim 5 recites "[t]he method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

325. NCT-377 discloses that the VIEW2 clinical study will last at least a year. (Ex.1015, NCT-377, 6 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) ***during the first year***." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week

dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48 (red arrows):




(Ex.1001, '338 patent, Fig.1 (modifications added)).

326. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claim 5 is anticipated by NCT-377.

**4. Dependent claims 6 and 7 are anticipated by NCT-377.**

327. Claim 6 of the '338 patent recites the method of claim 1, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

328. Claim 7 further limits the method of claim 6 to "wherein the angiogenic eye disorder is age related macular degeneration."

329. NCT-377 discloses the title of the clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and

Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4). NCT-377 thus discloses the treatment of AMD, which was known to be an angiogenic eye disorder.

330. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 6 and 7 are anticipated by NCT-377.

**5. Dependent claims 8-10 are anticipated by NCT-377.**

331. Claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

332. Claim 9 depends from claim 8 and specifies that all doses be administered by "intraocular administration."

333. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

334. NCT-377 discloses the title of the VIEW2 clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of *Intravitreal* VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4 (emphasis added)). NCT-377 thus expressly discloses intravitreal administration.

335. Therefore, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that claims 8-10 are anticipated by NCT-377.

**6. Dependent claims 11 and 13 are anticipated by NCT-377.**

336. Dependent claim 11 further limits the method of claim 10 to "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

337. Claim 13 depends from claim 11 and recites "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

338. NCT-377 discloses that subjects in one of the VIEW2 treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). NCT-377 thus expressly discloses the claimed doses.

339. Accordingly, for these reasons, as well as for the reasons discussed above for claim 1 and the claims from which claims 11 and 13 depend, it is my opinion that claims 11 and 13 are anticipated by NCT-377.

**7. Independent claim 14 is anticipated by NCT-377.**

340. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

341. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 315-19), it is also my opinion that NCT-377 discloses these identical elements in claim 14.

342. Second, in my opinion, NCT-377 discloses the VEGF antagonist element of claim 14. Just as for claim 1, NCT-377 expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1006, Dixon, 1575-76, Fig.1; Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094).

343. Thus, for these reasons, as well as the reasons set forth above for claim 1, it is my opinion that claim 14 is anticipated by NCT-377.

**8. Dependent claims 16 and 17 are anticipated by NCT-377.**

344. Claim 16 depends from claim 14 and recites "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose."

345. Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

346. As discussed with respect to claims 3 and 4 above, NCT-377 discloses the elements of claims 16 and 17. NCT-377 states that subjects in one of the four VIEW2 treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). In my opinion, this VIEW2 dosing schedule consists of an "initial" 2.0 mg dose, a first "secondary" 2.0 mg dose at week 4, a second "secondary" 2.0 mg dose at week 8, and "tertiary" 2.0 mg doses every 8 weeks for the remainder of the year.

347. For these reasons, as well as the reasons discussed above for claim 14, it is my opinion that claims 16 and 17 are anticipated by NCT-377.

### 9. Dependent claims 18 and 20 are anticipated by NCT-377.

348. Claim 18 depends from claim 17, which ultimately depends from claim 14 and recites "wherein the angiogenic eye disorder is age related macular degeneration."

349. Claim 20 recites the method of claim 14, "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

350. As discussed with claims 6 and 7 above, NCT-377 discloses the title of the VIEW2 clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4). NCT-377 therefore expressly discloses treating AMD, which was known to be an angiogenic eye disorder.

351. Therefore, for these reasons, as well as the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that claims 18 and 20 are anticipated by NCT-377.

### 10. Dependent claim 19 is anticipated by NCT-377.

352. Dependent claim 19 further limits the method of claim 14 to "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately

preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

353. As discussed with claim 5, NCT-377 discloses that the VIEW2 clinical study will last at least a year. (Ex.1015, NCT-377, 6 ("2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) ***during the first year***." (emphasis added))). As illustrated in my modified Figure 1 of the '338 patent, an 8-week dosing interval over the course of one year, after the initial dose and 2 secondary doses, would result in at least 5 tertiary doses administered at least 8 weeks after the immediately preceding dose, at weeks 16, 24, 32, 40, and 48.

354. Accordingly, for these reasons, as well as the reasons discussed above for claims 5 and 14, it is my opinion that claim 19 is anticipated by NCT-377.

**11. Dependent claims 21-23 are anticipated by NCT-377.**

355. Dependent claim 21 further limits the method of claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

356. Claim 22 depends from claim 21 and specifies that all doses be administered by "intraocular administration."

357. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

358. As discussed with claims 8-10 above, NCT-377 discloses the title of the VIEW2 clinical study as "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of *Intravitreal* VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4 (emphasis added)). NCT-377 therefore expressly discloses intravitreal administration.

359. Thus, for these reasons, as well as the reasons discussed above for claims 8-10 and 14, it is my opinion that claims 21-23 are anticipated by NCT-377.

**12. Dependent claims 24 and 26 are anticipated by NCT-377.**

360. Claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist."

361. Claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

362. As discussed with claims 11 and 13 above, NCT-377 discloses that subjects in one of the VIEW2 treatment arms will receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4) during the first year." (Ex.1015, NCT-377, 6). NCT-377 therefore expressly discloses the claimed doses.

363. Accordingly, for these reasons, as well as the reasons set forth above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that claims 24 and 26 are anticipated by NCT-377.

### F. Claims 1, 3-11, 13, 14, 16-24, and 26 of the '338 Patent Are Obvious in View of Dixon, Either Alone or in Combination with the '758 Patent or Dix.

#### 1. Independent claim 1.

364. I have set forth above the disclosures in Dixon that I believe anticipate the challenged claims, and I incorporate those disclosures herein. In my opinion, in addition to anticipating the challenged claims, Dixon also would make the subject matter of the challenged claims obvious.

365. First, one of ordinary skill in the art would have been motivated to explore dosing regimens that reduce the frequency of intravitreal injections administered in a monthly dosing scheme. This was a widely discussed concern at the time, and is evident from the Dixon reference itself. (Ex.1006, Dixon, 1574, 1577 (noting the "time and financial burden of monthly injections" and "[d]esirable attributes for emerging therapies for neovascular AMD include . . . decreased dosing intervals")).

366. Second, one of ordinary skill in the art would have observed in Dixon, and in the many other publicly available reports of the initiation of the VIEW Phase 3 trials, that a solution to the dosing frequency issue was presented therein in the

form of the publicly disclosed VIEW regimens involving every-8-week dosing following three monthly loading doses. (*Id.* at 1576).

367. Third, one of ordinary skill in the art would have had a reasonable expectation of success using the VIEW regimens for treating AMD. Dixon, in addition to reporting on the Phase 3 VIEW regimens, also provides a summary of the Phase 2 VEGF Trap-Eye results. For example, Dixon reports that the Phase 2 PRN regimen of 2.0 mg doses resulted in a mean increase of 9.0 ETDRS letters, with 29% gaining greater than or equal to 15 ETDRS letters at 52 weeks. (*Id.*). Those patients also experienced a mean decrease in retinal thickness of 143 μm. (*Id.*). A comparison to the results eventually reported for VIEW1/VIEW2 further illustrates why a person of ordinary skill in the art would have been justified in having a reasonable expectation of success based on the Phase 2 data:

| Measure | Phase 2<br>4 monthly + PRN<br>(as reported in Dixon) | Phase 3 (VIEW1, VIEW2)<br>3 monthly + every-8-week<br>(as reported in Heier-2012) |
|---|---|---|
| BCVA letter gain | +9.0 | +7.9, +8.9 |
| Retinal thickness (μm) | -143 | -128.5, -149.2 |
| Number of doses<br>(first year) | 5.6 | 8 |

368. As Dixon further notes, patients on the Phase 2 PRN regimen received, on average, 1.6 doses during the PRN dosing phase. (*Id.*). This means that, combined with the 4 monthly loading doses, patients in this group received, on average, 5.6 doses over the course of the first year. On the other hand, a patient would receive 8 doses in the first year under the Phase 3 VIEW dosing regimen (3 monthly loading doses followed by 5 every-8-week doses (i.e., doses at months 0, 1, 2, 4, 6, 8, 10, and 12)). The reasonable expectation of success is confirmed by Regeneron itself, who stated that the Phase 2 studies "indicat[e] that an 8-week dosing schedule may be feasible." (Ex.1036, Regeneron (28-April-2008), 1). Indeed, after the Phase 2 results, Regeneron did in fact go with the 3 monthly loading dose/every-8-week dosing regimen for its Phase 3 trial. In my opinion, Regeneron would not have settled on that regimen without having a reasonable expectation that it would be successful. In sum, it is my opinion that a person of ordinary skill in the art, in light of the Phase 2 results, would have indeed had a reasonable expectation of success that the Phase 3 regimen would be capable of treating AMD.

369. Fourth, with respect to the amino acid sequence and protein domains recited in claim 1, I discuss these disclosures in depth in the sections above and incorporate that discussion into this analysis. VEGF Trap-Eye/aflibercept was a well-known molecule among those of ordinary skill in the art, and a description of its molecular structure and sequence could be found throughout the prior art. (*See,*

*e.g.*, Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1093).

370. Accordingly, it is my opinion that the disclosures of Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 1 of the '338 patent obvious.

**2. Dependent claims 3 and 4.**

371. Dependent claim 3 limits the method of claim 1 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." And, claim 4 further limits the method of claim 3 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

372. As discussed above, Dixon discloses the elements of claim 3 (each secondary dose is administered 4 weeks after the immediately preceding dose) and claim 4 (each tertiary dose is administered 8 weeks after the immediately preceding dose) in the discussion of the VIEW study arms. (*See, e.g.*, Ex.1006, Dixon, 1576 ("2.0 mg at an 8 week dosing interval (following three monthly doses)")).

373. Accordingly, and for the reasons discussed above with respect to claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 3 and 4 of the '338 patent obvious.

**3. Dependent claim 5.**

374. Claim 5 claims the method of claim 1, "wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

375. Dixon discloses that the VIEW1 and VIEW2 clinical trials were to last at least a year. (Ex.1006, Dixon, 1576 ("*After the first year* of the study, patients will enter a second year of p.r.n. dosing . . . . [T]he primary outcome will be the proportion of patients who maintain vision *at week 52* . . . ." (emphasis added)). As discussed above in the anticipation section, over the course of a year, and following the three monthly doses, the "8 week dosing interval" disclosed in Dixon for the VIEW studies would result in "at least 5 tertiary doses," administered at weeks 16, 24, 32, 40, and 48.

376. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 5 of the '338 patent obvious.

**4. Dependent claims 6 and 7.**

377. Claim 6 is dependent on claim 1 and recites "wherein the angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD. Claim 7, which depends from claim 6, recites "wherein the angiogenic eye disorder is age related macular degeneration."

378. The Dixon reference is drawn to disclosures of VEGF Trap's use in treating AMD, which was known to be an angiogenic eye disorder. Dixon reported on the results of the Phase 1 and Phase 2 VEGF Trap-Eye AMD studies and set forth the dosing regimens being tested in the Phase 3 AMD trial, including the dosing regimen of 3 monthly doses followed by every-8-week dosing. (*See, e.g.*, Ex.1006, Dixon, 1576).

379. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and

nucleotide sequences in the '758 patent and Dix, makes claims 6 and 7 of the '338 patent obvious.

**5. Dependent claims 8-10.**

380. Dependent claim 8 depends from claim 1 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

381. Claim 9 depends from claim 8 and specifies intraocular administration.

382. Claim 10 depends from claim 9 and specifies that "the intraocular administration is intravitreal administration."

383. Dixon expressly discloses that the VEGF Trap was intravitreally administered, reporting that the VIEW1 and VIEW2 Phase 3 studies "will evaluate the safety and efficacy of ***intravitreal*** VEGF Trap-Eye." (Ex.1006, Dixon, 1575-76 (emphasis added)). Intravitreal injection is a type of intraocular administration—more specifically, administration directly into the vitreous of the eye.

384. Thus, for these reasons, as well as for the reasons discussed above for claim 1, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 8-10 of the '338 patent obvious.

### 6. Dependent claims 11 and 13.

385. Dependent claim 11 depends from claim 10 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 13 depends from claim 11 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

386. Dixon expressly discloses that the treatment arms in the VIEW studies will employ a 2.0 mg dose. (*See, e.g.*, Ex.1006, Dixon, 1576 (disclosing "intravitreal VEGF Trap-Eye at . . . 2.0 mg at an 8-week dosing interval (following three monthly doses)")).

387. Therefore, for these reasons, as well as the reasons set forth above for claims 1 and 10, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 11 and 13 of the '338 patent obvious.

### 7. Independent claim 14.

388. Claim 14 of the '338 patent is identical to claim 1 with the only exception being in the third "wherein" clause.

389. First, claim 14 recites the same dosing regimen as that recited in claim 1: "wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered at least 8 weeks after

the immediately preceding dose." Thus, for the same reasons discussed above with respect to claim 1, (*see* ¶¶ 364-70), it is also my opinion that Dixon discloses these identical elements in claim 14.

390. Second, as discussed above, in my opinion, Dixon discloses the VEGF antagonist element of claim 14. Just as for claim 1, Dixon expressly discloses VEGF Trap-Eye/aflibercept, and the sequence aspect of claim 14 was widely published in the prior art. (*See, e.g.*, Ex.1010, '758 patent, Fig.24A-C (disclosing the nucleotide sequence and deduced amino acid sequence, as well as a description of each molecular component therein (i.e., the signal sequence, the FLT1 Ig domain 2, the FLK1 Ig domain 3, and the FcΔC1 domain), 10:15-17 (specifying that this molecule is termed "VEGFR1R2-FcΔC1(a)."); Ex.1033, Dix, [0013]-[0014], [0030]; Ex.1039, '095 patent, 1:45-54; Ex.1021, 2009 10-Q, 20 (using VEGF Trap and aflibercept interchangeably and explaining that "VEGF Trap-Eye is a specially purified and formulated form of VEGF Trap for use in intraocular applications"); Ex.1007, Adis, 261 (indicating in the title that aflibercept, VEGF Trap (R1R2), and VEGF Trap-Eye, among other terms, are understood by a person of ordinary skill in the art to refer, interchangeably, to the same drug); Ex.1094). Therefore, for the same reasons discussed above, it is my opinion that this aspect of claim 14 is obvious.

391. Therefore, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 14 of the '338 patent obvious.

**8. Dependent claims 16 and 17.**

392. Claim 16 limits the method of claim 14 to "wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose." Claim 17 further limits the method of claim 16 to "wherein each tertiary dose is administered 8 weeks after the immediately preceding dose."

393. I note that aside from the independent claims from which they depend, claims 16 and 17 are similar to claims 3 and 4. Accordingly, for the reasons discussed above for claim 14 and for claims 3 and 4, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 16 and 17 of the '338 patent obvious.

**9. Dependent claims 18 and 20.**

394. Claim 18 is dependent on claim 17, which ultimately depends from claim 14, and recites "wherein the angiogenic eye disorder is age related macular degeneration." Claim 20 is dependent on claim 14 and recites "wherein the

angiogenic eye disorder is selected from the group consisting of" several well-known eye disorders, including AMD.

395. Aside from the independent claims from which they depend, claim 18 is similar to claim 7 and claim 20 is similar to claim 6. Accordingly, for the reasons discussed above for claims 6, 7, 14, 16, and 17, it is my opinion that the disclosures of Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 18 and 20 of the '338 patent obvious.

**10. Dependent claim 19.**

396. Claim 19 claims the method of claim 14, "wherein at least 5 tertiary doses" are administered, and "wherein the first four tertiary does are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose."

397. Aside from the independent claims from which they depend, claim 19 is similar to claim 5. Accordingly, for the reasons discussed above for claims 5 and 14, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claim 19 of the '338 patent obvious.

### 11. Dependent claims 21-23.

398. Dependent claim 21 depends from claim 14 and recites "wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration."

399. Claim 22 depends from claim 21 and specifies intraocular administration.

400. Claim 23 depends from claim 22 and specifies that "the intraocular administration is intravitreal administration."

401. Aside from the independent claims from which they depend, claims 21-23 are similar to claims 8-10. Accordingly, for the reasons discussed above for claims 8-10, and 14, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 21-23 of the '338 patent obvious.

### 12. Dependent claims 24 and 26.

402. Dependent claim 24 depends from claim 23 and recites "wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist." Dependent claim 26 depends from claim 24 and specifies "wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist."

403. Aside from the independent claims from which they depend, claims 24 and 26 are similar to claims 11 and 13. Accordingly, for the reasons discussed above for claims 11 and 13, and the claims from which claims 24 and 26 depend, it is my opinion that Dixon, either alone, or in combination with the disclosures of the VEGF Trap domain architecture and VEGF Trap amino acid and nucleotide sequences in the '758 patent and Dix, makes claims 24 and 26 of the '338 patent obvious.

## IX. SECONDARY CONSIDERATIONS.

404. I understand that a patent owner may in some circumstances rely on so-called "secondary considerations of non-obviousness" to attempt to refute a finding of obviousness of a claim.[23] I also understand that there are several categories of secondary considerations, which might include alleged unexpected results or a "long-felt but unmet need." Notwithstanding that the unpatentability of the challenged claims is supported by strong evidence, including the numerous Regeneron disclosures and public announcements of its dosing regimens for VEGF Trap-Eye/aflibercept well prior to the filing date of the '338 patent, it is my opinion that there are no unexpected results or a "long-felt but unmet need" that would refute the strong case of obviousness against the challenged claims.

[23] I understand that any showing of "secondary considerations" by the patent owner is not relevant to an anticipation analysis.

405. For example, I was asked to review Regeneron's statement to the U.S. Patent and Trademark Office, dated September 11, 2015. Therein, Regeneron argues that "improved unexpected results" were observed and thereafter described in the working examples of the '338 patent and a 2012 publication reporting on the results of the VIEW studies (Ex.1019, Heier-2012). Regeneron characterizes the standard of care prior to the filing of the '338 patent as once per month dosing. (Ex.1017, '338 FH, 9/11/2015 Remarks, 6). They further characterize the results reported in Heier-2012 as surprising, dramatic, and unexpected since the every-eight-week dosing group exhibited outcomes similar to those receiving monthly injections.

406. First, I note that the applicants admit that the VIEW1/2 every-8-week dosing regimen falls squarely within the scope of the claims of the '338 patent. This is the same regimen that was disclosed and disseminated before the filing date of the '338 patent, as I discuss at length above. (*See, e.g.*, Ex.1006, Dixon; Ex.1007, Adis; Ex.1013, Regeneron (8-May-2008); Ex.1014, NCT-795; Ex.1015, NCT-377; and the detailed discussion above of the disclosures of the VIEW1 and/or VIEW2 studies in each of these references).

407. Second, in my experience and that a person of ordinary skill in the art, as of 2010, monthly dosing was not the regimen typically used in standard clinical practice. By 2010, as I discuss above, the discomfort, inconvenience, and risks

experienced by patients [24] receiving intravitreal injections led most in the ophthalmology community to reduce the frequency of administration whenever possible. For example, my typical practice, together with the typical practice of the skilled person, when administering intravitreal anti-VEGF agents, involved the administration of a few loading dose injections, typically spaced a month apart. Thereafter, we would usually bring back patients for monthly visits to assess visual acuity and retinal swelling and only administer injections on those monthly visits where there appeared to be loss in visual acuity or increase in retinal swelling.

408. Third, in addition to that approach being common practice among practicing ophthalmologists and persons of ordinary skill in the art, it was the trend among industry leaders at the time as well. For example, after Genentech's monthly dosing studies of ranibizumab (MARINA and ANCHOR), they embarked on a clinical trial campaign directed to investigating dosing regimens with less frequent injections. For example, Genentech began, as early as 2007, to assess dosing

[24] This is a point on which I agree with Regeneron. (*See, e.g.*, Ex.1017, '338 FH, 9/11/2015 Remarks at 6 (stating that once-per-month injections are "(1) expensive; (2) painful to the patient; (3) inconvenient for the patient as well as the patient's family; (4) psychologically and physically traumatic to the patient; and (5) subjects the patient to potential adverse effects such as infection with each treatment event")).

regimens that included three monthly loading doses, followed by a period of individualized (i.e., as-needed/PRN) dosing, or fixed quarterly dosing. (*See, e.g.*, SUSTAIN (PRN dosing after 3 monthly loading doses); EXCITE (quarterly dosing after 3 monthly loading doses); PrONTO (PRN dosing after three monthly loading doses); SAILOR (PRN dosing after 3 monthly loading doses); and PIER (quarterly dosing after 3 monthly loading doses); Ex.1030, Mitchell, 6-7 (providing a summary of each of the above studies). From these studies, the authors concluded that while fixed quarterly dosing may be inferior to monthly dosing (though still more effective than placebo), the individualized regimens could achieve outcomes similar to that observed for monthly dosing. (*See, e.g.*, Ex.1030, Mitchell, 6-7).

409. Fourth, in my opinion, the results reported in Heier-2012, and which Regeneron relies upon in their remarks to the Patent Office, were not unexpected in light of the positive results reported for Regeneron's Phase 2 study of VEGF Trap-Eye in AMD. In that study, Regeneron used two treatment arms: (1) quarterly dosing for 12 weeks followed by PRN dosing; and (2) fixed monthly dosing for 12 weeks followed by PRN dosing. The latter group, when dosed with 2 mg, achieved on average a gain in visual acuity of 9 letters and a mean decrease in retinal thickness of 143 μm. (Ex.1006, Dixon, 1576). The results of the VIEW studies as reported in Heier-2012 included a mean gain in visual acuity of 7.9 letters and a mean decrease in retinal thickness of 128.5 μm. (Ex.1019, Heier-2012, 2542). In my opinion, these

results from the VIEW studies would not have been surprising or unexpected in light of the results reported for the Phase 2 CLEAR-IT-2 study. This is confirmed by Regeneron itself, who stated that the Phase 2 studies "indicat[e] that an 8-week dosing schedule may be feasible." (Ex.1036, Regeneron (28-April-2008), 1; *see also id.* ("Due to its high affinity for all isoforms of VEGF-A and PIGF . . . as well as its long residence time in the eye, it is anticipated that VEGF Trap-Eye may be able to be dosed at a frequency less than once monthly . . . . These emerging Phase 2 clinical data seem to support the concept of durability of VEGF Trap-Eye.")).

410. Lastly, I disagree that there were "an infinite number of different treatment protocols" when deciding on dosing regimens to investigate. Given the concern (shared by Regeneron) over the frequency of monthly dosing, monthly injections would have been avoided if possible, and anything more frequent than monthly would not have been reasonably considered by skilled artisans. The ranibizumab studies were showing that quarterly (i.e., every 3 month) regimens had trouble maintaining gains in visual acuity in some cases. As a result, if monthly was disfavored, and every 3 months was seen as less effective in some cases, a person of ordinary skill in the art naturally would have considered dosing every 2 months, which is precisely what Regeneron used in their VIEW studies. Regarding the number of loading doses, the trend in the industry was that three monthly loading doses could achieve substantial gains in visual acuity and decreases in retinal

thickness. (*See, e.g.*, Ex.1030, Mitchell, 6-7). Therefore, in my opinion, there was nothing new or non-obvious about the regimen Regeneron settled upon, and its claims to the Patent Office that there were "an infinite number of different treatment protocols" was not true given the state of the art and the practical realities of treating AMD patients with intravitreal injections.

411. In sum, a person of ordinary skill in the art would have expected the claimed dosing regimen to work based on the positive Phase 1 and Phase 2 trial results. Thus, it would have been expected that following the dosing regimen set forth in the '338 patent would have led to at least some level of "treating" an angiogenic eye disorder. The dosing regimens claimed in the '338 patent were not unexpected in my opinion, and the arguments presented by the patentees to the Patent Office do not support their claims of unexpected results.

412. Moreover, to the extent that the inventors would claim an unmet and long-felt need was fulfilled with the '338 patent, in my opinion, this is not the case. While I agree that there may have been a need for VEGF antagonists prior to their development, in my opinion, once those antagonists were developed, and especially after the dosing knowledge was gleaned from ranibizumab and the early trials of VEGF Trap-Eye, arriving at a dosing regimen that extended the administration beyond once-monthly was obvious, had already been noted in the literature and put into actual practice, and served no "unmet" need. This is particularly so given that

the dosing regimen was already publicly disclosed as early as 2009, meaning that any "unmet" need had already been met by Regeneron's own public disclosures well before the '338 patent was filed.

413. I further understand that there may be commercial products that the patent owner may attempt to assert are encompassed by the claims, one potential example being Eylea®. However, in my opinion, none of the claimed dosing regimens covered by the '338 patent that I have discussed above are responsible for any commercial success of Eylea®, and I have seen no evidence that the commercial success of Eylea® has been due to anything outside of marketing and promotional activities or regulatory exclusivity. To the extent that Regeneron or their technical expert raise secondary considerations arguments, I reserve the right to address and respond to those arguments in a future declaration.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that all of my statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 5/4/21

By: _____
Dr. Thomas A. Albini

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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*Inter Partes* Review No.: IPR2021-00881

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

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

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# DECLARATION OF MARY GERRITSEN, PH.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,254,338 B2

## TABLE OF CONTENTS

I, Mary Gerritsen, Ph.D., declare as follows:

## I. INTRODUCTION.

1. I submit this declaration on behalf of Mylan Pharmaceuticals Inc. ("Petitioner"). I understand that Petitioner is filing a petition with the United States Patent and Trademark Office ("USPTO") for *inter partes* review of U.S. Patent No. 9,254,338 B2 (the "'338 patent") (Ex.1001).

2. This Declaration contains my qualifications; my opinions based on my expertise, and my review of the '338 patent and other documents cited within this Declaration; the factual basis for those opinions; and data or other information I considered in forming my opinions. The opinions and facts set forth in this Declaration are based upon information and my analysis of documents related to the '338 patent, as well as my knowledge and experience in the pharmaceutical and biotechnology industries.

## II. QUALIFICATIONS.

3. I am a pharmacologist with over thirty years of experience in the pharmaceutical and biotechnology industries.

4. In 2010, I founded Gerritsen Consulting, and I have been a consultant for the biotechnology industry on topics related to biotherapeutics and drug discovery in the therapeutic areas of oncology, immuno-oncology, ophthalmology, autoimmune diseases/inflammation, cardiovascular disease, and angiogenesis-

related diseases. Specifically, I have collaborated with companies in numerous areas of product development, including research strategy, target selection and assessment, preclinical pharmacology and mechanism of action studies, preparation of Investigational New Drug applications, procedures for clinical trials, and evaluation of pipeline portfolio strategies.

5. Prior to my consulting work, I was the Vice President of Molecular and Cellular Pharmacology at Exelixis, Inc. from 2004-2010. Exelixis is a biotechnology company focused on the development of small molecular therapeutics for the treatment of oncology and metabolic disease. I supervised many of the processes involved in preclinical to early clinical development, including target identification and validation, early lead discovery and validation, lead optimization, cellular and molecular pharmacology studies, pharmacodynamic assays, and early translational medicine studies. I also collaborated with the clinical groups in the early stages of Phase I clinical trials.

6. From 2003-2004, I was a consultant with Frazier Health Care Ventures in which I was involved in the founding of MacuSight, Inc., a pharmaceutical company focused on angiogenesis disorders, specifically focused on age-related macular degeneration and diabetic macular edema. I was an inventor on several of the patents that were the basis for the foundation of the company which included U.S. Patent Nos. 8,222,271, 8,486,960, and 9,452,156.

7. From 2002-2003, I was the Senior Director, Vascular Biology with Millennium Pharmaceuticals (formerly COR Therapeutics) where I was responsible for development of the strategic plan for vascular biology and oversaw numerous small molecule development programs in the therapeutic indications of atherosclerosis, peripheral vascular disease, and fibrosis.

8. Prior to the above, I was Associate Director of the Department of Cardiovascular Research at Genentech, Inc. from 1997-2001. Separately, I was a senior investigator in the angiogenesis group whose focus was the identification of novel targets for protein-based therapeutics. Throughout my time at Genentech, I was involved in the drafting and filing of over 1,000 patent applications in which over forty such applications issued as patents.

9. Before joining Genentech, I was a Principal Staff Scientist and Group Leader, Institute for Inflammation and Autoimmunity at Bayer Pharmaceuticals (formerly Miles Pharmaceuticals) from 1990-1997. During this time, I led the screening efforts for small molecule inhibitors of leukocyte adhesion, cyclo-oxygenase, and cytokine release/action while also supervising six laboratories within the Institute. Additionally, I developed collaborations with other industrial development laboratories as well as academic laboratories in order to promote advances in target discovery and assay development.

10. Prior to my roles in the pharmaceutical and biotechnology industry, I received a Bachelor of Science degree in Zoology and a Ph.D. in Endocrinology and Pharmacology from the University of Calgary. I completed my post-doctoral studies in Pharmacology at the University of California, San Diego. Following my post-doctoral work, I was an Assistant and later an Associate Professor of Physiology at New York Medical College from 1980-1989. During this time, I conducted research in therapeutic areas including stroke, inflammation, ophthalmology, and diabetic vascular disease.

11. Throughout my career, I have more than 100 publications in peer-reviewed journals, written numerous book chapters, and authored three books. I am currently, or have been, a member of numerous professional organizations, and I have been presented with numerous awards and honors throughout my career.

12. Additional information about my professional and educational experience, and other background information, is described in my *curriculum vitae* (Ex.1061).

## III. SCOPE OF ENGAGEMENT.

13. I have been retained by Petitioner as a technical expert to offer my analysis and opinions regarding various issues related to certain prior art references as they relate to the '338 patent, discussed in more detail below.

14. My time spent on this project is compensated at $350 per hour. My compensation does not depend in any way on the outcome of Petitioner's petition for *inter partes* review of the '338 patent. Furthermore, I have no financial interest in this matter.

15. My opinions and views set forth in this Declaration are based on my education and training, my experience in academia and the pharmaceutical and biotechnology industries, and on the materials I have reviewed for this case.

16. I have reviewed the '338 patent and relevant sections of its prosecution history before the USPTO, (*see* Ex.1017, '338 FH). I have also reviewed and considered various other documents in arriving at my opinions, and cite them in this Declaration.

17. I have been asked to consider the level of education, skill set and training possessed by persons of ordinary skill in the field relevant to the '338 patent as of at least January 13, 2011.[1, 2]

18. I have also been asked to consider, from the perspective of the person of ordinary skill in the art as of at least January 13, 2011, whether certain references or documents were available as printed publications, or, in other words, whether certain references or documents would have been publicly accessible to persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, before 2011.

19. I have formed certain opinions on these issues, which I set forth in greater detail below. In sum, it is my opinion that each of the references I discuss in

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[1] I have been asked to assume that the priority date of the '338 patent is January 13, 2011, the date of the earliest filed provisional application that appears on the '338 patent cover page. However, I note that the Applicant of the application that issued as the '338 patent argued that the priority date of the '338 patent was November 2011. (*See* Ex.1017, '338 FH, 9/11/15 Amendment, 7). I have formed no opinion regarding the merit of the '338 patent's claim to any priority date.

[2] I provide my understanding of the qualifications for a person of ordinary skill in the art relevant to the '338 patent in ¶¶ 22-24, below.

this declaration are printed publications in that they were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before Jan. 13, 2011. Moreover, my opinions in this regard are repeatedly confirmed by other contemporaneous prior art documents, which expressly cite the references I have been asked to evaluate. (*See* ¶¶ 47, 54, 62, 73, 82-87, 97, below).

## IV. THE PERSON OF ORDINARY SKILL IN THE ART.

20. As I mentioned above, it is my understanding that my analysis is to be conducted from the perspective of a person of ordinary skill in the art at the time of the invention.

21. I also understand that in defining a person of ordinary skill in the art the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field.

22. I understand that a person of ordinary skill in the art is a hypothetical person who is presumed to be aware of all pertinent art, thinks along the lines of conventional wisdom in the art, and is a person of ordinary creativity at the time of the invention. I further understand that the relevant timeframe for assessing the '338

patent's claims from the perspective of a person of ordinary skill in the art is assumed to be January 13, 2011 (the earliest possible priority date for the '338 patent).

23. With respect to the '338 patent, a person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in: (i) developing treatments for angiogenic eye disorders, such as age-related macular degeneration ("AMD"), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

24. A person of ordinary skill in the art would have been aware of the references and teachings described below, as well as other important information and references relating to angiogenic eye disorders, the causes of said disorders, and useful treatments for said disorders.

## V. LEGAL STANDARDS.

25. I am not a lawyer and do not purport to offer any legal opinions. In forming my opinions set forth herein, I have been asked to apply certain standards regarding printed publications.

26. I understand that a reference, publication, document, etc. is a "printed publication" if the document is "publicly accessible." I also understand that a reference is considered "publicly accessible" if it was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.

27. Thus, a reference that could be classified as a "printed publication" before the priority date of the '338 patent would be considered prior art to the '338 patent.

## VI. U.S. PATENT NO. 9,254,338.

28. I understand that the '338 patent issued on February 9, 2016 to Regeneron Pharmaceuticals, Inc. and is titled "USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS," with George D. Yancopoulos listed as the sole inventor. (Ex.1001, '338 patent, cover). I also understand that the '338 patent issued from U.S. Application No. 13/940,370 ("the '370 Application"), a continuation-in-part of International Application No. PCT/US2012/020855, filed January 11, 2012, and claims priority to U.S. Provisional Application No.

61/432,245, filed on January 13, 2011, U.S. Provisional Application No. 61/434,836, filed on January 21, 2011, and U.S. Provisional Application No. 61/561,957, filed on November 21, 2011. (*Id.*).

29. I understand that the '338 patent contains two independent claims and twenty-four dependent claims. The independent claims are listed below:

> **1**. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457of SEQ ID NO:2.

> **14**. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

(Ex.1001, '338 patent, 23:2-18; *id.*, 24:3-15 (emphasis added to highlight the differences between the claims)). Claim 14 is very similar to claim 1 with the only difference (highlighted in yellow) being that the VEGF antagonist (aflibercept) is described by reference to the nucleic acid SEQ ID NO rather than the amino acid SEQ ID NO as in claim 1. (*Id.*). I also understand that claims 2-13 depend from claim 1, directly or indirectly (*id.*, 23:19-24:2), and claims 15-26 depend from claim 14, directly or indirectly (*id.*, 24:16-53).

## VII. PROSECUTION HISTORIES OF THE '338 PATENT AND ITS EUROPEAN EQUIVALENT, EP-325.

30. I have reviewed the prosecution history for the '338 patent, which I understand appears at Ex.1017. It is my understanding that the '370 Application was filed on July 12, 2013 (Ex.1017, '338 FH, 7/12/2013 Transmittal of New Application, 1) and originally included twenty claims directed towards a method of treating "an angiogenic eye disorder" with a "VEGF antagonist." (*Id.*, 7/12/2013 Original Application, 22-23).

31. I have also reviewed EP 2 663 325 (Ex.1062, EP-325), which appears to be the European equivalent to the '370 Application, which issued as the '338 patent. (*Id.*, cover). EP-325 claims the same priority chain as the '370 Application—specifically, EP-325 claims priority to International Application No. PCT/US2012/020855, filed January 11, 2012, that claims priority to U.S. Provisional Application No. 61/432,245, filed on January 13, 2011, U.S. Provisional

Application No. 61/434,836, filed on January 21, 2011, and U.S. Provisional Application No. 61/561,957, filed on November 21, 2011. (*Id.*).

32. As originally filed, it is my understanding that EP 325 included claims similar to those prosecuted in the '370 Application that issued as the '338 patent. (*See id.*, [0020]-[0024]; Ex.1063, EP-325-FH, 7/5/2013 Amendments, 19-20; Ex.1017, '338 FH, 7/12/2013 Original Application, 22-23). I have prepared the following chart to illustrate the similarities between the '370 Application claims and the EP 325 claims:

| **'370 Application Original Claims** | **EP-325 Original Claims** |
|---|---|
| 1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; | 1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist; |
| wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and | wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and |
| wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose. | wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose. |
| 2. The method of claim 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks | 2. The method of claim 1, wherein only a single secondary dose is administered to the patient, and wherein the single secondary dose is administered 4 weeks |

| '370 Application Original Claims | EP-325 Original Claims |
|---|---|
| after the initial dose of the VEGF antagonist. | after the initial dose of the VEGF antagonist. |
| 3. The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose. | 3. The method of claim 1, wherein only two secondary doses are administered to the patient, and wherein each secondary dose is administered 4 weeks after the immediately preceding dose. |
| 4. The method of claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose. | 4. The method of claim 3, wherein each tertiary dose is administered 8 weeks after the immediately preceding dose. |
| 5. The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose. | 5. The method of claim 1, wherein at least 5 tertiary doses of the VEGF antagonist are administered to the patient, and wherein the first four tertiary doses are administered 8 weeks after the immediately preceding dose, and wherein each subsequent tertiary dose is administered 8 or 12 weeks after the immediately preceding dose. |

| '370 Application Original Claims | EP-325 Original Claims |
|---|---|
| 6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization. | 6. The method of claim 1, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization. |
| 7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration. | 7. The method of claim 6, wherein the angiogenic eye disorder is age related macular degeneration. |
| 8. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor-based chimeric molecule. | 8. The method of claim 1, wherein the VEGF antagonist is an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody or fragment thereof, or a VEGF receptor based chimeric molecule. |
| 9. The method of claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule. | 9. The method of claim 8, wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule. |
| 10. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1. | 10. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1. |
| 11. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a | 11. The method of claim 9, wherein the VEGF receptor-based chimeric molecule comprises (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a |

| '370 Application Original Claims | EP-325 Original Claims |
|---|---|
| multimerization component comprising amino acids 232-457 of SEQ ID NO:2. | multimerization component comprising amino acids 232-457 of SEQ ID NO:2. |
| 12. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration. | 12. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration. |
| 13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration. | 13. The method of claim 12, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration. |
| 14. The method of claim 13, wherein the intraocular administration is intravitreal administration. | 14. The method of claim 13, wherein the intraocular administration is intravitreal administration. |
| 15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration. | 15. The method of claim 11, wherein all doses of the VEGF antagonist are administered to the patient by topical administration or by intraocular administration. |

| '370 Application Original Claims | EP-325 Original Claims |
|---|---|
| 16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration. | 16. The method of claim 15, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration. |
| 17. The method of claim 16, wherein the intraocular administration is intravitreal administration. | 17. The method of claim 16, wherein the intraocular administration is intravitreal administration. |
| 18. The method of claim 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist. | 18. The method of claim 17, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist. |
| 19. The method of claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist. | 19. The method of claim 18, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist. |
| 20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist. | 20. The method of claim 18, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist. |

(Ex.1017, '338 FH, 7/12/2013 Original Application, 22-23; Ex.1063, EP-325-FH, 1/23/2012 Claims, 19-20).

33. As I describe in more detail in the following paragraphs, several references were cited as prior art against EP-325, confirming, in my opinion their public availability and relevance to the '338 patent.

34. According to the prosecution history of EP-325, the International Searching Authority identified a September 28, 2008 Regeneron Press Release as a

"prior art document" that it "considered" in its May 22, 2012 written opinion (referencing the document as "D13")):

D13: XP002674126

Thomson Reuters Integrity: "VEGF Trap-Eye final phase II results in age-related macular degeneration presented at 2008 Retina Society Meeting",
,
28 September 2008 (2008-09-28), pages 1-1, XP002674126,

**D13** (phase II study) describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by an 40 additional weeks-treatment on a PNR (as needed) dosing schedule.

(Ex.1063, EP-325-FH, 5/14/2012 International Searching Authority Written Opinion, 3-4; *id.*, 7/19/2012 International Search Report, 1; *see also id.*, 9/5/2016 Third Party Observations, 2 (D13)). The International Search Authority then continued to discuss "D13" as the "closest prior art":

7.1 **The closest prior art, D13** (phase II study summary), describes the improvement of visual acuity in age-related macular degeneration patients after VEGF Trap-Eye monthly or quarterly administration for 12 weeks followed by 40 additional weeks treatment on a PNR (as needed) dosing schedule.

(*Id.*, 5/14/2012 International Searching Authority Written Opinion, 5).

35. The European Patent Office cited to this same Regeneron Press Release (as "D13") in reaching its conclusions in its August 21, 2014 Communication:

| | |
|---|---|
| 7.6 | **The problem to be solved** *"provision of improved protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization"* has not been shown to be solved by the claimed solutions in the present application. The objective technical problem needs to be reformulated to the less ambitious one *"provision of alternative protocols to treat age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion and corneal neovascularization"* for which the claimed solutions are obvious in view of D13. |

(Ex.1063, EP-325-FH, 8/21/2014 Communication, 8; *see also id.*, 3-5).

36. Indeed, multiple Third-Party Observations were submitted during prosecution of EP 325. The first Third Party Observation included reference to, among other things, Regeneron Press Releases, a ClinicalTrials.gov record (VIEW2 study), and Regeneron's Form 10-Q from November 2007—all submitted as "prior art":

| | |
|---|---|
| *D13:* | XP002674126 |
| *OBS1:* | Slides for the 2008 Retina Society Meeting "VEGF Trap-Eye in Wet AMD CLEAR-IT 2: Summary of One-Year Key Results", September 28, 2008 |
| *OBS2:* | Information from ClinicalTrials.gov archive on the VIEW 2 study (NCT00637377) version available on 17 March 2008 |
| *OBS3:* | Regeneron Pharmaceuticals, Inc. FORM 10-Q, published on 7 November 2007 for the period ending 30 September 2007 |
| *OBS4:* | WHO Drug Information, Vol.20, No. 2, 2006, pages 115-119 |
| *OBS5:* | Dixon et al., Expert Opin. Investig. Drugs (2009) 18 (10): 1-8 |
| *OBS6:* | Simó and Hernández, Diabetes Care, Volume 32, Number 8, August 2009 |
| *OBS7:* | Mousa and Mousa, Biodrugs 2010; 24(3); 183-194 |
| *OBS8:* | Regeneron, Press release "Regeneron Reports First Quarter 2008 Financial and Operating Results", May 1, 2008 |

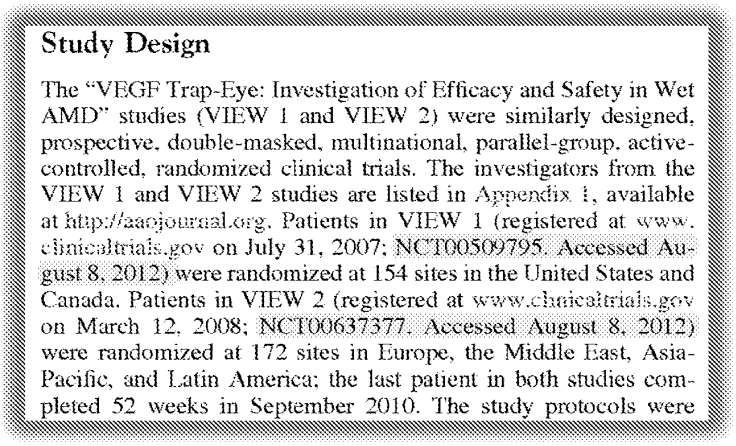
(Ex.1063, EP-325-FH, 9/5/2016 Third Party Observations, 2; *see also id.*, 3-4). The second Third Party Observation additionally identified the following:

| | |
|---|---|
| Annex 1 | Press Release of Regeneron dated 22 November 2010 |
| Annex 2 | Press Release of Regeneron dated 20 December 2010 |
| Annex 3 | Article in Retinal Physician (March 2010) |

(*Id.*, 9/7/2016 Third Party Observations, 2).

37. The European Patent Office's and Third Parties' reliance on the above-mentioned documents confirms, in my opinion, that each was publicly accessible in that they were disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, could locate them. I further note that, as far as I can tell from reviewing the EP-325 file history, Regeneron never contested the public availability of those documents.

38. Separately, I find it important to note that, while prosecuting the '338 patent, the Applicants relied extensively on Heier-2012, a reference that, in my opinion, further confirms the public accessibility of Petitioner's asserted ClinicalTrials.gov reports, NCT-795, and NCT-377:



Study Design

The "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD" studies (VIEW 1 and VIEW 2) were similarly designed, prospective, double-masked, multinational, parallel-group, active-controlled, randomized clinical trials. The investigators from the VIEW 1 and VIEW 2 studies are listed in Appendix 1, available at http://aaojournal.org. Patients in VIEW 1 (registered at www.clinicaltrials.gov on July 31, 2007; NCT00509795. Accessed August 8, 2012) were randomized at 154 sites in the United States and Canada. Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008; NCT00637377. Accessed August 8, 2012) were randomized at 172 sites in Europe, the Middle East, Asia-Pacific, and Latin America; the last patient in both studies completed 52 weeks in September 2010. The study protocols were

(Ex.1018, Heier-2012, 2539; *see also* Ex.1017, '338 FH, 9/11/2015 Amendment, 7 ("The attached Heier et al. article is a peer reviewed article published in 'Ophthalmology . . . .'")).

## VIII. DISCLOSURES, KNOWLEDGE, & INFORMATION AVAILABLE IN THE ART BEFORE JANUARY 13, 2011.

### A. REGENERON PRESS RELEASES.

39. In my experience in the pharmaceutical and biotechnology industries, companies like Regeneron and Bayer routinely issue press releases that include information on product development and/or clinical trials. These press releases can include information regarding, among other things, the specific product in development, the study design of a clinical trial, and preliminary or final results from a specific clinical trial or trials. A person of ordinary skill in the art would be interested in this type of information regarding ongoing product development within the industry, including information regarding the development of products of a direct

competitor. For example, this type of information continually updates the competitive landscape for a particular market and would assist the person of ordinary skill in the art in evaluating the same. As these press releases are a rich source of information about the ongoing development for a particular treatment, persons of ordinary skill in the art routinely review such press releases, whether as a result of exercising diligence, received from email alerts (e.g., Google Alerts), or website updates (e.g., Seeking Alpha, Evaluate Pharma, and FiercePharma). Indeed, I myself have searched for, reviewed and relied upon such press releases throughout my professional career.

40. Regeneron's and Bayer's press releases regarding VEGF Trap-Eye were no different, and, in my opinion, a person of ordinary skill in the art would have sought out this information. As specifically noted below, the Regeneron and Bayer press releases regarding VEGF Trap-Eye disclosed the ongoing development of VEGF Trap-Eye as a therapy for angiogenic eye disorders, including different treatment regimens using VEGF Trap-Eye.

41. Not only would a person of ordinary skill in the art have been interested in, and sought out, the information contained in the Regeneron and Bayer press releases, but this person would have been able to easily obtain these press releases directly from Regeneron's website on the date of each release. In fact, companies routinely publish press releases and other information on the company website under

a "News" menu or something similar (e.g., "Media" menu or "Investors & Media" menu) in order to disseminate them to the public in an easily accessible manner. Press releases are well-known to the community interested in the subject matter of the reference as a source of useful information. Additionally, documents such as press releases typically appear in web search results when a person of ordinary skill in the art conducts a search using various search engines (e.g., via Google, Google Scholar).

42. Thus, as of the date of each press release, a person of ordinary skill in the art would have been able to locate the specific press release on, among other things, Regeneron's website exercising reasonable diligence, easily access each press release via Regeneron's website, and easily download an electronic copy.

**1. April 2008 Press Release.**

43. Regeneron and Bayer HealthCare AG issued a press release dated April 28, 2008, (Ex.1012, Regeneron (28-April-2008)), which described the thirty-two week results from a "double-masked, prospective, randomized, multi-center Phase 2 trial" in patients with the "neovascular form of Age-related Macular Degeneration (wet AMD)," treated with VEGF Trap-Eye. (*Id.*, 1).

44. The patients in the study were "randomized to five dose groups" as follows:

(1) monthly dose of 0.5 milligrams (mg) of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

(2) monthly dose of 2.0 mg of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

(3) quarterly dose of 0.5 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule;

(4) quarterly dose of 2.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule; or

(5) quarterly dose of 4.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule.

(*Id.*, 1-2).

45. Regeneron (28-April-2008) added that VEGF Trap-Eye was being evaluated "using a monthly loading dose of . . . 2.0 mg for 12 weeks, followed by a nine-month fixed-dosing regimen of . . . 2.0 mg every eight weeks." (*Id.*, 1-2).

46. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (28-April-2008) included the experimental group that received VEGF Trap-Eye 2.0 mg every eight weeks following 3 monthly "loading dose" injections. (*Id.*, 1-2).

47. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (28-April-2008) because it

pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (*Id.*, 1). My opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis (Ex.1007, Adis) provides the following among twenty separate references to online "Media Releases":

> 14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration. Media Release: 29 Apr 2008. Available from URL: http://www.regeneron.com

(*Id.*, 268 (emphasis added)). Indeed, press releases such as Regeneron (28-April-2008) were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g.*, *id.*, 262-63, 268-69).

48. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (28-April-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[3] Thus, a person of

[3] *See, e.g.*, Ex.1012, Regeneron (28-April-2008), 1.

ordinary skill in the art could have easily accessed Regeneron (28-April-2008) via Regeneron's website and easily downloaded an electronic copy.

49. For at least these reasons, it is my opinion that Regeneron (28-April-2008) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

**2. May 2008 Press Release.**

50. Regeneron and Bayer HealthCare AG issued a press release dated May 8, 2008 (Ex.1013, Regeneron (8-May-2008)) which described the phase 3 age-related macular degeneration VIEW 2 clinical trial. (*Id.*, 1; *see also* Ex.1032, Bayer (8-May-2008), 1).[4]

51. Specifically, Regeneron (8-May-2008) stated that both the complete VIEW 1 trial and the VIEW 2 trial were "designed to evaluate the efficacy and safety of VEGF Trap-Eye administered by intravitreal injection, at dosing intervals of 4 and 8 weeks." (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1).

[4] I note that the information disclosed within the Regeneron Press Releases discussed herein is essentially the same as the information disclosed within the corresponding Bayer Press Releases.

52. Regeneron (8-May-2008) also described the dosing regimens used in the VIEW 2 clinical trial, including "2.0 mg at an 8-week dosing interval, including one additional 2.0 mg dose at week four" in which one of the dosing arms included a regimen of 2 mg every 8 weeks, with an additional injection at week 4. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1-2).

53. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in Regeneron (8-May-2008) included the experimental group that received VEGF Trap-Eye 2 mg every other month following 3 initial monthly injections. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1-2).

54. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (8-May-2008) because it pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with age-related macular degeneration. (Ex.1013, Regeneron (8-May-2008), 1; Ex.1032, Bayer (8-May-2008), 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":

12. Bayer HealthCare AG. Bayer and Regeneron start additional Phase 3 Study for VEGF Trap-Eye in Wet Age-related Macular Degeneration. Media Release: 8 May 2008. Available from URL: http://www.bayerscheringpharma.de

13. Bayer HealthCare AG, Regeneron Pharmaceuticals Inc. Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age-Related Macular Degeneration. Media Release: 8 May 2008. Available from URL: http://www.bayerhealthcare.com

(Ex.1007, Adis, 268 (emphasis added); *see also* Ex.1032, Bayer (8-May-2008), 1). Indeed, press releases such as Regeneron (8-May-2008) were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g.*, *id.*, 262-63, 268-69).

55. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (8-May-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[5] Thus, a person of ordinary skill in the art could have easily accessed Regeneron (8-May-2008) via Regeneron's website and easily downloaded an electronic copy.

[5] *See, e.g.*, Ex.1013, Regeneron (8-May-2008), 1.

56. For at least these reasons, it is my opinion that Regeneron (8-May-2008) and Bayer (8-May-2008) were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

**3. September 2008 Press Release.**

57. Regeneron and Bayer HealthCare AG issued a press release dated September 28, 2008 (Ex.1056, Regeneron (28-September-2008)) which described the final results for the same "double-masked, prospective, randomized, multi-center Phase 2 trial" in patients with wet age-related macular degeneration, treated with VEGF Trap-Eye that was described in Regeneron (28-April-2008). (*Id.*, 1).

58. As noted above, the patients in the study were "randomized to five dose groups" as follows:

(1) monthly dose of 0.5 milligrams (mg) of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

(2) monthly dose of 2.0 mg of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

(3) quarterly dose of 0.5 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule;

(4) quarterly dose of 2.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule; or

(5) quarterly dose of 4.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule.

(Ex.1056, Regeneron (28-September-2008), 1).

59. Regeneron (28-September-2008) stated that "[p]atients receiving monthly doses of VEGF Trap-Eye of either 2.0 or 0.5 milligrams (mg) for 12 weeks followed by PRN dosing achieved mean improvements in visual acuity versus baseline" and "mean decreases in retinal thickness versus baseline." (Ex.1056, Regeneron (28-September-2008), 1).

60. Regeneron (28-September-2008) also described the dosing regimens used in the two Phase 3 trials, VIEW1 and VIEW2, including "VEGF Trap-Eye dosed . . . 2 mg every 8 weeks (following three monthly doses)." (Ex.1056, Regeneron (28-September-2008), 1-2).

61. A person of ordinary skill in the art would have understood the dosing regimens disclosed in Regeneron (28-September-2008) included the experimental groups that were to receive VEGF Trap-Eye 2 mg every 8 weeks (following three monthly doses) or "monthly doses of 0.5 or 2.0 milligrams (mg) of VEGF Trap-Eye" followed by "a PRN dosing schedule based upon the physician assessment of the need for re-treatment." (Ex.1056, Regeneron (28-September-2008), 1-2).

62. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in Regeneron (28-September-2008) because it

pertains to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (Ex.1056, Regeneron (28-September-2008), 1). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adi provides the following among twenty separate references to online "Media Releases":

> 14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration. Media Release: 29 Apr 2008. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron (28-September-2008) were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g., id.*, 262-63, 268-69).

63. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate Regeneron (28-September-2008) exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter

contained therein without further research or experimentation.[6] Thus, a person of ordinary skill in the art could have easily accessed Regeneron (28-September-2008) via Regeneron's website and easily downloaded an electronic copy.

64. For at least these reasons, it is my opinion that Regeneron (28-September-2008) was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

**4. Additional Regeneron Press Releases.**

65. Regeneron and Bayer HealthCare AG issued a press release dated March 27, 2007 (Ex.1053, Regeneron (27-March-2007)), which described the twelve-week data for a "Phase 2 randomized study of their VEGF Trap-Eye in patients with the neovascular form of age-related macular degeneration (wet AMD)." (*Id.*, 1).

66. The patients in the study were "randomized to 5 groups" where "[t]wo groups received either 0.5 or 2.0 mg of VEGF Trap-Eye administered every four weeks, and three groups received a single dose of 0.5, 2.0, or 4.0 mg of VEGF Trap-Eye." (Ex.1053, Regeneron (27-March-2007), 1). Furthermore, the President of Regeneron Research Laboratories was quoted as stating "[o]ur Phase 3 program is

[6] *See, e.g.*, Ex.1056, Regeneron (28-September-2008), 1.

being designed to test this possibility and further evaluate the safety and efficacy of various doses and dosing intervals of the VEGF Trap-Eye." (*Id.*).

67. Regeneron and Bayer HealthCare AG issued a press release dated August 2, 2007 (Ex.1054, Regeneron (2-August-2007)) which described "a Phase 3 study of the VEGF Trap-Eye in the neovascular form of age-related macular degeneration (wet AMD)." (*Id.*, 1). Specifically, Regeneron (2-August-2007) described "VEGF Trap-Eye . . . doses . . . 2.0 mg at an eight-week dosing interval." (*Id.*).

68. Regeneron and Bayer HealthCare AG issued a press release dated August 19, 2008 (Ex.1089, Regeneron (19-August-2008)), which described the 52-week data for the same "double-masked, prospective, randomized, multi-center Phase 2 trial" in patients with "wet age-related macular degeneration (AMD)" treated with VEGF Trap-Eye that was described in Regeneron (28-April-2008). (*Id.*, 1; *see also* Ex.1092, Bayer (19-August-2008), 1).

69. As noted above, the patients in the study were "randomized to five dose groups" as follows:

(1) monthly dose of 0.5 milligrams (mg) of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

(2) monthly dose of 2.0 mg of VEGF Trap-Eye for twelve weeks followed by therapy at the same dose on a PRN dosing schedule;

(3) quarterly dose of 0.5 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule;

(4) quarterly dose of 2.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule; or

(5) quarterly dose of 4.0 mg of VEGF Trap-Eye (at baseline and week 12) followed by therapy at the same dose on a PRN dosing schedule.

(Ex.1089, Regeneron (19-August-2008), 1; Ex.1092, Bayer (19-August-2008), 1-2).

70. Regeneron (19-August-2008) also described the dosing regimens used in the two Phase 3 trials, VIEW 1 and VIEW 2, including "VEGF Trap-Eye dosed . . . 2 mg every 8 weeks (following three monthly doses)." (Ex.1089, Regeneron (19-August-2008), 1; Ex.1092, Bayer (19-August-2008), 2-3).

71. Regeneron issued a press release dated September 14, 2009 (Ex.1068, Regeneron (14-September-2009)), which described two "Phase 3 clinical trials evaluating VEGF Trap-Eye in the treatment of the neovascular form of age-related macular degeneration (wet AMD)." (*Id.*, 1). Specifically, Regeneron (14-September-2009) described "VEGF Trap-Eye . . . dosed . . . 2.0 mg every eight weeks (following three monthly doses)." (*Id.*).

72. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in at least Regeneron (19-August-2008) and Regeneron (14-September-2009) included the experimental group that was to receive VEGF

Trap-Eye "2 mg every 8 weeks (following three monthly doses)." (Ex.1089, Regeneron (19-August-2008), 1; *see also* Ex.1068, Regeneron (14-September-2009), 1 ("2.0 mg every eight weeks (following three monthly doses)").

73. A person of ordinary skill in the art would have been interested in, and sought out, the information disclosed in the above Press Releases because they pertain to ongoing product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (*See* ¶¶ 40-41, 47, 54, 62, above). Again, my opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly refer to similar Regeneron and Bayer press releases. For example, Adis provides the following among twenty separate references to online "Media Releases":

> 14. Regeneron Pharmaceuticals Inc, Bayer HealthCare AG. Regeneron and Bayer HealthCare Announce Encouraging 32-Week Follow-Up Results from a Phase 2 Study of VEGF Trap-Eye in Age-Related Macular Degeneration. Media Release: 29 Apr 2008. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added)). Indeed, press releases such as Regeneron's Press Releases were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See, e.g., id.*, 262-63, 268-69).

74. In my opinion (and as confirmed by, e.g., Adis), a person of ordinary skill in the art would have also been able to locate these Regeneron Press Releases exercising reasonable diligence, which would have at least led the person of ordinary

skill in the art to Regeneron's website where these documents were easily accessible and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[7] Thus, a person of ordinary skill in the art could have easily accessed these Press Releases via Regeneron's website and easily downloaded an electronic copy.

75. For at least these reasons, it is my opinion that Regeneron's Press Releases outlined above were well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

### B. CLINICALTRIALS.GOV.

76. ClinicalTrials.gov is an electronic registry and results database of clinical studies supported by the U.S. National Institutes of Health that is open and accessible to the public as a "resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and

[7] *See, e.g.*, Ex.1053, Regeneron (27-March-2007), 1; Ex.1054, Regeneron (2-August-2007), 1; Ex.1089, Regeneron (19-August-2008), 1; Ex.1068, Regeneron (14-September-2009), 1.

conditions."[8] Each study record includes a summary of the study protocol. ClinicalTrials.gov includes records for several clinical studies involving aflibercept, namely VIEW1 (ClinicalTrials.gov identifier NCT00509795) (Ex.1014, NCT-795), and VIEW2 (ClinicalTrials.gov identifier NCT00637377) (Ex.1015, NCT-377).

77. In my experience, ClinicalTrials.gov is a reliable and trustworthy source for information about scheduled, ongoing, and completed clinical trials. The information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study.[9] Clinical trials are submitted to the site when they begin, and the information on the site is updated throughout the study.[10] Indeed, I myself have searched for, reviewed and relied upon the information found in numerous clinical trials through ClinicalTrials.gov. Furthermore, a person of ordinary skill in the art considers the posting dates cited at ClinicalTrials.gov to be trustworthy and authoritative.

78. NCT-795 was first available as of at least August 1, 2007 and describes a clinical study titled "A Randomized, Double Masked, Active Controlled Phase III Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal

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[8] Ex.1069, Background-ClinicalTrials.gov.

[9] *Id.*

[10] *Id.*

VEGF Trap in Subjects With Neovascular Age-Related Macular Degeneration." (Ex.1014, NCT-795, 3; Ex.1087, Wayback-Affidavit-038 (Wayback Machine records showing public availability of NCT-795 prior to Jan. 13, 2011); Ex.1018, Heier-2012, 2539 ("Patients in View 1 (registered at www.clinicaltrials.gov on July 31, 2007 . . . )")). NCT-795 lists the following experimental "arms" of the study:

| | |
|---|---|
| Experimental Arm 1: aflibercept injection 0.5mg (VEGF Trap-Eye) | 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. |
| Experimental Arm 2: aflibercept injection 2.0mg (VEGF Trap-Eye) | 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. |
| Experimental Arm 3: aflibercept injection 2.0mg (VEGF Trap-Eye) | 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. |

(Ex.1014, NCT-795, 6-8 (Experimental Arms 1-3)). The experimental arms above included the group which required participants to receive "2.0 mg VEGF Trap-Eye

administered every 8 weeks (including one additional 2.0 mg dose at week 4) during the first year." (*Id.*, 8).

79. NCT-377 was first available as of at least March 18, 2008 and describes a clinical study titled "A Randomized, Double Masked, Active Controlled, Phase 3 Study of the Efficacy, Safety, and Tolerability of Repeated Doses of Intravitreal VEGF Trap in Subjects With Neovascular Age-related Macular Degeneration (AMD)." (Ex.1015, NCT-377, 3-4; Ex.1087, Wayback-Affidavit-038 (Wayback Machine records showing public availability of NCT-377 prior to Jan. 13, 2011); *see also* Ex.1018, Heier-2012, 2539 ("Patients in VIEW 2 (registered at www.clinicaltrials.gov on March 12, 2008 . . . )")). NCT-377 lists the following experimental "arms" of the study:

| | |
|---|---|
| Experimental Arm 1: Aflibercept Injection (VEGF Trap-Eye) | 0.5 mg VEGF Trap-Eye administered every 4 weeks during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. |
| Experimental Arm 2: Aflibercept Injection (VEGF Trap-Eye) | 2.0 mg VEGF Trap-Eye administered every 4 weeks during the first year. |

| | |
|---|---|
| | Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. |
| Experimental Arm 3: Aflibercept Injection (VEGF Trap-Eye) | 2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year. Thereafter a dose may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks. |

(Ex.1015, NCT-377, 6 (Experimental Arms 1-3)). The experimental arms above included the group which required participants to receive "2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2,0 mg dose at Week 4) during the first year." (*Id.*, 1).

80. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in NCT-795 and NCT-377 included the experimental group that received VEGF Trap-Eye 2.0 mg every two months "including one additional 2.0 mg dose at Week 4." (Ex.1014, NCT-795, 8; *see also* Ex.1015, NCT-377, 6).

81. A person of ordinary skill in the art would have been interested in and easily accessed and sought out the information disclosed on the ClinicalTrials.gov

website regarding NCT-795 and NCT-377 because it pertains to ongoing routine product development within the industry, including dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with wet AMD. (Ex.1014, NCT-795, 6-8; Ex.1015, NCT-377, 6). Thus, in my opinion, NCT-795 and NCT-377 were both "publicly accessible" as they were disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, could locate them.

82. My opinion in this regard is, in fact, confirmed by other contemporaneous prior art to the '338 patent that expressly cited to clinical trial records from ClinicalTrials.gov, including both NCT-795 and NCT-377. For example, Reichert (Ex.1072, Reichert)[11] provides the following disclosures of NCT-795 and NCT-377:

[11] Ex.1072, Reichert, 76; *see also id.*, cover (Reichert is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

> (Lucentis®, Genentech). In the 4 arm VIEW 1 study [NCT00509795], adult patients (50 years and older) in arms 1 and 2 are administered either 0.5 or 2.0 mg aflibercept every four weeks for 1 year, then the same dose is administered as frequently as every four weeks but no less frequently than every 12 weeks. Patients

(*Id.*, 94 (emphasis added)); and

> is September 2013. The on-going VIEW 2 [NCT00637377] has the same design as VIEW 1, but is being conducted at sites in Europe, Asia Pacific, Japan and Latin America by Bayer. A total of 1,211 patients were recruited; the estimated study completion date is August 2011.

(*Id.*, 95 (emphasis added); *see also id.*, 96). Moreover, Reichert makes multiple, express references to obtaining information online directly from ClinicalTrials.gov. (*Id.*, 79 (Table 7 ("listed on clinicaltrials.gov")); *id.*, 99 (Ref. No. 69 (citing ClinicalTrials.gov record and corresponding internet address))).

83. Similarly, Anderson (Ex.1073, Anderson)[12] provides the following disclosures of NCT-795 and NCT-377 online reports:

> Two phase III clinical trials are underway (VIEW-1 in the USA and Canada and VIEW-2 in Europe, Asia-Pacific, Japan and Latin America). These non-inferiority studies aim to compare efficacy of VEGF Trap against ranibizimab. Study completion is expected in 2012 and 2011, respectively (http://clinicaltrials.gov/ct2/show/NCT00509795; http://clinicaltrials.gov/ct2/show/NCT00637377). The effect of VEGF Trap on DMO is in phase II clinical testing (http://clinicaltrials.gov/ct2/show/NCT00789477). Table 1 also

(*Id.*, 275 (emphasis added)). Anderson made additional references to obtaining information from ClinicalTrials.gov. (*Id.*, 272-77, 280; *see also id.*, 373 (Figure 1 ("Graph displaying the number of clinical trials registered with the ClinicalTrials.gov registry (http://clinicaltrials.gov) each year between 2001 and 2009."))).

84. Another example, Ciulla (Ex.1074, Ciulla),[13] provides the following:

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[12] Ex.1073, Anderson, 272 (Anderson is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

[13] Ex.1074, Ciulla, 158 (Ciulla is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

52 ($P < 0.0001$ for both from baseline). Currently, two randomized, international phase III studies (VIEW-1 and VIEW-2) (http://www.clinicaltrials.gov; NCT00509795, NCT00637377) are comparing intravitreal VEGF trap with ranibizumab.

(*Id.*, 162 (emphasis added)). Ciulla also made numerous other references to ClinicalTrials.gov and obtaining information from that database. (*Id.*, 162-63).

85. Ni (Ex.1075, Ni)[14] provides the following:

27 Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects with Wet AMD (VIEW 1). http://www.clinicaltrials.gov/ct2/show/NCT00509795?order=1 (accessed July 31, 2007).

28 Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2). http://clinicaltrials.gov/ct2/show/NCT00637377?order=1 (accessed March 12, 2008).

(*Id.*, 409 (emphasis added)). Additionally, Ni references numerous clinical trials with citations to ClinicalTrials.gov as the source of the information. (*See id.*, 408-10).

[14] Ex.1075, Ni, 401 (Ni is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

86. Another example, Zarbin (Ex.1076, Zarbin),[15] provided the following:

> in a Phase 1 clinical trial.[150] VEGF Trap-Eye (http://clinicaltrials.gov/ct2/show/NCT00509795?term=VEGF+Trap-Eye&rank=14) is formulated for intravitreal injection, appears to be effective in a Phase 2 trial (www.bmctoday.net/retinatoday/2009/10/article.asp?f=1009_08.php), and is now being compared with ranibizumab in a Phase 3 clinical trial. AAV2-sFLT01

(*Id.*, 1360 (emphasis added)). Additionally, Zarbin also references numerous clinical trials with citations to ClinicalTrials.gov as the source of the information. (*See id.*, 1351-52, 1356-62).

87. Dixon (Ex.1006, Dixon)[16] provides the following citations, further confirming that both NCT-795 and NCT-377, including the dosing regimens disclosed therein, were publicly available as of at least September 28, 2008:

[15] Ex.1076, Zarbin, 1350 (Zarbin is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

[16] Ex.1006, Dixon, 1573 (Dixon is a printed publication that was publicly available prior to January 13, 2011, and would be considered prior art to the '338 patent).

46. Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects With Wet AMD (VIEW 1) [ClinicalTrials.gov identifier: NCT00509795] ClinicalTrials.gov [online]. Available from: http//clinicaltrials.gov/ct2/show/NCT00509795 [Accessed 28 Sep 2008]

47. VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2). [ClinicalTrials.gov identifier: NCT00637377] ClinicalTrials.gov [online]. Available from: http//clinicaltrials.gov/ct2/show/NCT00637377 [Accessed 28 Sep 2008]

(*Id.*, 1579 (emphasis added)). Accordingly, it is my firm opinion that ClinicalTrials.gov records, NCT-795 and NCT-377, were well-known—and widely available—to the community interested in the subject matter of the '338 patent.

88. Prior to 2011, a person of ordinary skill in the art would have also been able to locate both NCT-795 and NCT-377 exercising reasonable diligence and which would have at least led the person of ordinary skill in the art to the ClinicalTrials.gov website where the documents were easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[17] Thus, a person of ordinary

[17] *See* Ex.1014, NCT-795, 1; Ex.1015, NCT-377, 1.

skill in the art of the '338 patent could have easily accessed both NCT-795 and NCT-377 via ClinicalTrials.gov and easily downloaded an electronic copy of each.

89. For the reasons outlined above, a person of ordinary skill in the art would have considered the posting dates cited at ClinicalTrials.gov to be trustworthy and authoritative and it is my opinion that NCT-795 and NCT-377 were both well-known, printed publications that were publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

C. SEC FILINGS.

90. As I note above (*see* ¶¶ 39-41), company press releases were well-known, and widely available, to persons of ordinary skill in the art. This was especially true of persons of ordinary skill in the art of the '338 patent, who expressly cited Bayer and Regeneron press releases. (*See, e.g.*, Ex.1007, Adis, 262-63, 268-69).

91. Moreover, domestic publicly-traded companies are required to file certain forms with the SEC, and this is well-known by those in the pharmaceutical industry and academia. A company's SEC filings provide reliable information about a company that allows a person in the art to ensure that they are well informed and up-to-date on all of the most important developments. (Ex.1077, Corporate Finance Institute; *see also* Ex.1078, Schneider, 258 (noting that "SEC filings . . . have been

considered to be among the most accurate and reliable . . . sources of information available"); Ex.1079, Kuepper).

92. SEC filings, such as a company's Form 10-Q, are easily accessible via the Electronic Data Gathering, Analysis, and Retrieval system ("EDGAR") or a company's website. (*See, e.g.*, Ex.1080, Zucchi). SEC filings provide, among other things, information regarding the company's finances as well as recent business activity. (*See id.*; Ex.1081, Hayes).

93. In my experience in the industry, SEC filings for pharmaceutical or biotechnology companies included information regarding ongoing development of different products, including ongoing clinical trials and the results of completed clinical trials. Thus, in my opinion, a person of ordinary skill in the art would utilize the information contained therein, amongst other references, to keep up to date on the development in the field of interest, especially with direct competitors.

94. First, a person of ordinary skill in the art would be interested in such "Financial and Operating Results," for example, SEC filings, as confirmed by the prior art:

> 8. Regeneron Pharmaceuticals Inc. Regeneron Reports Second Quarter Financial and Operating Results; BLA Filing for Auto-Inflammatory Diseases Planned for Early 2007; Two Antibody Candidates from VelocImmune(R) Program to Enter Clinical Trials Each Year Beginning in 2007. Media Release: 3 Aug 2006. Available from URL: http://www.regeneron.com

(Ex.1007, Adis, 268 (emphasis added); *see also id.* (Ref. Nos. 6, 18)).

95. Second, in my opinion and as I noted above, a person of ordinary skill in the art would have been aware of such company filings, such as Regeneron's September 30, 2009 10-Q (Ex.1021, 2009 10-Q), and would routinely look to 10-Q filings to determine what drugs and treatments pharmaceutical companies were working on. Here, Regeneron disclosed information regarding, among other things, its ongoing development of the VEGF Trap-Eye program—specifically focused on the clinical trials for VEGF Trap-Eye—in its September 30, 2009 10-Q. (*Id.*, 20 ("The VIEW 1 and VIEW 2 trials are both evaluating VEGF Trap-Eye doses of . . . 2.0 mg at a dosing interval of eight weeks (after three monthly doses)."). 2009 10-Q also disclosed results of the CLEAR-IT trial, which included "monthly doses of VEGF Trap-Eye of . . . 2.0 . . . mg for 12 weeks followed by PRN dosing," and the DA VINCI trial. (*Id.*, 19-20).

96. A person of ordinary skill in the art would have understood that the dosing regimens disclosed in 2009 10-Q included the experimental group that received VEGF Trap-Eye 2.0 mg every eight weeks following three monthly "loading dose" injections or "monthly doses of VEGF Trap-Eye of . . . 2.0 . . . mg for 12 weeks followed by PRN dosing." (Ex.1021, 2009 10-Q, 19-20).

97. Thus, in my opinion, a person of ordinary skill in the art also would have been interested in, and sought out, the information disclosed in 2009 10-Q because it pertains to ongoing product development within the industry, including

dosing regimens of a known therapy (VEGF Trap-Eye or aflibercept) in patients with angiogenic eye disorders such as wet AMD. (Ex.1021, 2009 10-Q, 19-20). My opinion in this regard is confirmed by other contemporaneous prior art to the '338 patent which expressly refer to the Regeneron 2010 Financial Press Release which, in turn, directed a person of ordinary skill in the art to Regeneron's company filings with the SEC. (*See* Ex.1007, Adis, 268 (Ref. Nos. 6, 18)). Indeed, company filings such as 2009 10-Q were well-known—and widely available—to the community interested in the subject matter of the '338 patent. (*See id.*, 262-63, 268 (Reference Nos. 6, 18)).

98. It is also my opinion that 2009 10-Q would have been routinely available to a person of ordinary skill in the art. Prior to 2011, a person of ordinary skill in the art would have been able to locate 2009 10-Q exercising reasonable diligence, which would have at least led the person of ordinary skill in the art to Regeneron's website where the document was easily accessible, and recognize and comprehend therefrom the essentials of the subject matter contained therein without further research or experimentation.[18] Thus, a person of ordinary skill in the art could have easily accessed 2009 10-Q via Regeneron's website and easily downloaded an electronic copy.

[18] *See* Ex.1021, 2009 10-Q.

99. For at least these reasons, it is my opinion that 2009 10-Q was a well-known, printed publication that was publicly accessible to persons interested and ordinarily skilled in the subject matter or art of the '338 patent, exercising reasonable diligence, before 2011.

## IX. CONCLUDING STATEMENTS.

100. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the USPTO Patent Trial and Appeal Board. I acknowledge that I may be subject to cross-examination in this case. If cross-examination is required of me, I will appear for cross-examination during the time allotted for such cross-examination.

101. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: April 26, 2021

Mary Gerritsen, Ph.D.

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

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

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# EXPERT DECLARATION OF DR. DIANA V. DO, M.D.

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I, Dr. Diana Do, declare as follows:

## I. INTRODUCTION

1. I have been retained by counsel for Regeneron Pharmaceuticals, Inc. ("Regeneron") as a technical expert in connection with the above-captioned proceeding. I have been asked to provide my opinions and views on the materials I have reviewed in relation to the Petition for *Inter Partes* review ("IPR") of U.S. Patent No. 9,254,338 (the "'338 patent") (Ex. 1001), in particular how a person of skill in the art as of the filing date of the '338 patent would understand certain terms of the '338 patent claims, and responses to the opinion and views of Petitioner's declarant, Dr. Thomas A. Albini. I submit this declaration in support of Regeneron's Patent Owner Preliminary Response ("POPR"). I reserve the right to provide further and additional opinions in the event that IPR is instituted.

2. I am being paid at an hourly rate for my work on this matter. I have no personal or financial stake in the outcome of the present proceeding.

## II. QUALIFICATIONS AND EXPERIENCE

3. I am a Professor of Ophthalmology and the Vice Chair for Clinical Affairs at the Byers Eye Institute at Stanford University School of Medicine and have been since 2017. I also serve as a Physician Improvement Leader at Byers Eye Institute, a position I have held since 2018. I have an active clinical and surgical practice and I work as a clinical investigator to study novel treatments for retinal diseases. In addition, I teach students, residents, and retina fellows at Stanford and

am a member of the Stanford Ophthalmology Education Committee.

4. I graduated from the University of California Berkeley (summa cum laude) with a B.A. degree in Molecular and Cellular Biology in 1995 and earned my M.D. (Alpha Omega Alpha) from the University of California San Francisco School of Medicine in 1999. Following medical school, I completed an internship in internal medicine at Massachusetts General Hospital at Harvard Medical School. From 2000-2003, I completed my residency in Ophthalmology at the Wilmer Eye Institute at Johns Hopkins University School of Medicine, and then remained at the Wilmer Eye Institute for a Retina Fellowship in surgical and medical retina from 2003-2005.

5. From 2005 through 2010, I served as Assistant Professor of Ophthalmology and Assistant Head of the Retina Fellowship Training Program at the Wilmer Eye Institute. In 2011, I was promoted to Associate Professor and Head of the Retina Fellowship Training Program, positions I held through 2013.

6. In 2013, I joined the faculty at the Truhlsen Eye Institute at the University of Nebraska College of Medicine, where I became a full Professor of Ophthalmology in 2015. At the Truhlsen Eye Institute, I was Head of the Retina Fellowship Training Program and Program Director for the Ophthalmology Residency. In my leadership roles at the Truhlsen Eye Institute, I also served as Vice Chair of Education. I was recruited by Stanford University's Ophthalmology

Department (the Byers Eye Institute) at Stanford in the beginning of 2017.

7. As a physician-scientist, I am an international leader in the treatment of diabetic retinopathy and wet AMD ("wAMD"). My research has led to more than 140 peer-reviewed publications. My research interest focuses on evaluating the efficacy and safety of novel pharmacologic therapies for diabetic macular edema, diabetic retinopathy, wAMD, retinal vein occlusion, and ocular inflammation. I have led national and global clinical trials investigating intravitreal VEGF inhibitors (aflibercept and ranibizumab) for diabetic eye disease and wet AMD. Our research developed a greater understanding of how intraocular inhibition of VEGF reduces vascular permeability and angiogenesis in diabetic eye disease, thereby reducing diabetic macular edema and improving visual acuity. Before the onset of pharmacologic therapies, thermal laser photocoagulation was the only treatment option for diabetic macular edema and laser was not effective in improving vision. Our research led to new treatment paradigms and better vision outcomes for patients with diabetic macular edema, diabetic retinopathy, and wAMD. The results from the collaborative research that I led has revolutionized how ophthalmologists throughout the world think about and treat patients with VEGF-mediated retinal diseases.

8. Since 2009, I have been the lead investigator and a Steering Committee member for the evaluation of aflibercept, a fusion protein that inhibits VEGF, in

diabetic macular edema. I initiated the first-in-human clinical trial of aflibercept. In addition, I also was the principal investigator on the Phase II and III clinical trials of aflibercept for diabetic macular edema to further evaluate efficacy, dosing regimens, and safety. My leadership in these global clinical trials, which enrolled over 1,000 subjects, contributed to FDA approval of aflibercept for diabetic macular edema. Aflibercept has also been approved by FDA for other angiogenic ocular diseases such as wAMD, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

9. My research efforts have also led to a greater understanding of the role of ranibizumab, an intravitreal VEGF antibody fragment biologic, in diabetic macular edema. I was a lead investigator in the Ranibizumab for Edema of the Macula in Diabetes (READ) Study Group and was the lead author on multiple manuscripts evaluating the efficacy and safety of ranibizumab. The collaborative studies that I led contributed to understanding dosing regimens for intravitreal VEGF inhibitors, and led to the design of pivotal clinical trials involving ranibizumab for diabetic macular edema. Ranibizumab was the first FDA approved intravitreal VEGF inhibitor for diabetic macular edema, and helped to transform the management of diabetic retinopathy. I continue to lead clinical trials investigating new treatments for retinal diseases.

10. As a result of my research, I am recognized as an international thought

leader on the subject of the retina and am regularly invited to lecture and teach at international and national meetings including the American Academy of Ophthalmology Retina Sub-Specialty Meeting, American Society of Retina Specialists, Asian Pacific Vitreo-Retinal Society Meeting, Canadian Ophthalmology Society Meeting, and congresses throughout Europe. I have organized and participated as a faculty member in national continuing medical education courses to teach my retina colleagues how to manage and treat diabetic macular edema, wet AMD, retinal vein occlusion, diabetic retinopathy, and other retinal disorders. Furthermore, I have held leadership positions at the American Society of Retina Specialists (Communications Committee Member to curate and develop online educational material), Women in Retina (Board Member and Secretary), Maryland Eye Society (President).

11. I am a practicing ophthalmologist with over 15 years of clinical and surgical practice in retina. I am a leader in the management of diabetic retinopathy, the leading cause of blindness in working age adults, and wAMD, the leading cause of vision loss in elderly individuals in developed countries. I have a high-volume clinical and surgical practice and spend approximately 1.5 days per week in clinic at the Byers Eye Institute and half-day per week at the Santa Clara Valley County Medical Center seeing patients in my clinical practice. In addition, I operate approximately one day per week at the Byers Eye Institute.

12. Given my extensive experience and research on diabetic retinopathy and wAMD, I have become the expert retinal specialist and surgeon in our department for evaluating these chronic eye diseases. Since joining Stanford's Ophthalmology Department, I have also become one of the highest volume retina surgeons among our faculty. Because proliferative diabetic retinopathy can lead to tractional retinal detachment and bleeding within the eye, I am referred complex cases that often require clinic-based treatments (such as intravitreal injections of medicines or pan retinal laser photocoagulation) or surgical management. Since I have clinical and research expertise using intravitreal vascular endothelial growth factor (VEGF) inhibitors in wAMD, ophthalmologists refer patients to me for consultation or co-management, particularly of chronic cases that have not responded to therapy. The majority of my patients are from the Bay Area or central California, and approximately 10% travel from more than 5 hours away to seek my expert opinion. I have been recognized as a "Top Doctor" in the Bay Area for the past three years.

13. A current copy of my curriculum vitae is included at Ex. 2002.

## III. SUMMARY OF OPINIONS

14. My opinions and views set forth in this declaration are based on my education, training, research, and clinical experience in ophthalmology, specifically in researching and treating retinal diseases, as well as the materials I reviewed in

preparing this declaration and the state of scientific knowledge in the art pertaining to the subject matter of the '338 patent at the time of its earliest priority application.

15. In forming my opinions, I have reviewed the following materials: (a) the Petition for *Inter Partes* Review of the '338 patent, IPR2021-00881, including all cited exhibits, (b) all priority applications leading to the issuance of the '338 patent, (c) all other documents and references herein, and (d) the Patent Owner's Preliminary Response to which my declaration relates.

16. It is my opinion, for at least the reasons set forth below, that the preamble language of Claims 1 and 14 requires treatment of an angiogenic eye disorder.

17. Further it is my opinion, for the reasons set forth below, that "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."

## IV. THE PERSON OF ORDINARY SKILL IN THE ART

18. For the limited purpose of preparing this declaration in support of Patent Owner's Preliminary Response, I have been asked to apply Dr. Albini's definition of a person of ordinary skill in the art (who I also refer to as the "skilled artisan"):

> [A] person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or

> published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in: (i) developing treatments for angiogenic eye disorders, such as AMD, including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.

Ex. 1002, ¶ 28.

19. Applying Dr. Albini's definition a person of ordinary skill in the art, I would have been at least a skilled artisan when the '338 patent was filed.

20. Likewise, for the purpose of preparing this declaration, I have been informed and understand that the earliest filing date of the '338 patent is January 13, 2011, based on the filing of a Provisional Application on that date.

## V. THE '338 PATENT

21. I understand that Petitioner has challenged claims 1, 3-11, 13-14, 16-24 and 26 of the '338 patent.

### A. Claim 1

22. The '338 patent has two independent claims, claim 1 and 14.

23. Claim 1 recites:

> A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.

Ex. 1001 at 23:1-18.

24. The dosing regimen of Claim 1 is directed to the treatment of any type of angiogenic eye disorder with a VEGF antagonist that has a particular amino acid sequence.

25. The dosing regimen of Claim 1 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more "secondary" doses administered two to four weeks after the preceding dose, and then one or more "tertiary" doses that are administered at least eight weeks following the preceding dose.

26. Challenged claims 3-11 and 13 depend from Claim 1, and further limit the timing between dosage administration, the specific angiogenic eye disorder, administration route, and dosage amount.

**B. Claim 14**

27. Claim 14 recites:

> A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
>
> wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
>
> wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
>
> wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising VEGFR1R2-FcΔC1(a) encoded by the nucleic acid sequence of SEQ ID NO:1.

Ex. 1001 at 24:3-15.

28. The dosing regimen of Claim 14 is directed to the treatment of any type of angiogenic eye disorder with a particular VEGF antagonist that is encoded by the recited nucleic acid sequence.

29. Like Claim 1, the dosing regimen of Claim 14 requires treatment of an angiogenic eye disorder by administration of an initial dose of the claimed VEGF antagonist followed by one or more "secondary" doses administered two to four weeks after the preceding dose, and then one or more "tertiary" doses that are administered at least eight weeks following the preceding dose.

30. Thus, Claim 14 differs from Claim 1 only with respect to the last

"wherein clause" specifying the nucleic acid sequence of SEQ ID NO:1. I understand that SEQ ID NO:2 is the corresponding amino acid sequence of the nucleic acid sequence SEQ ID NO:1.

31. Challenged Claims 16-24 and 26 depend from Claim 14, and further limit the timing between dosage administration, the specific angiogenic eye disorder, administration route, and dosage amount.

## VI. LEGAL FRAMEWORK

32. For purposes of this declaration, I have been informed by counsel for Patent Owner about certain aspects of the law that are relevant to my analysis and opinions.

33. I understand from counsel for Patent Owner that patent claim terms are construed from the vantage point of a skilled artisan to which the invention relates at the time of the invention (or as of the effective filing date of the patent application).

34. I am informed by counsel that claim terms should be considered in the context of the entire patent claim where they appear, as well as in the context of the other claims, the specification, and the prosecution history of the patent at issue (collectively, "intrinsic evidence"), taken as a whole (as opposed to in isolation and/or out of context).

35. I am advised by counsel that absent an explicit statement to the contrary by the patent applicant, a patent claim term should have its full ordinary and customary meaning and not be limited to a specific example that may appear in the patent specification as referring to a preferred embodiment.

36. I have been informed that where a term has no ordinary and customary meaning to those of ordinary skill in the prior art, one looks to the specification in the patent.

37. I am advised it is only necessary to construe terms that are in controversy, and only to the extent necessary to resolve the controversy.

## VII. CLAIM CONSTRUCTION

38. I have been asked to consider the meaning of "[a] method for treating an angiogenic eye disorder in a patient" and "tertiary dose(s)" from the perspective of a skilled artisan as of January 13, 2011, and respond to Dr. Albini's opinions regarding the meaning of these terms.[1]

### A. "A method for treating an angiogenic eye disorder in a patient"

39. The preamble of Claims 1 and 14 recites "[a] method for treating an angiogenic eye disorder in a patient." Ex. 1001 at 23:2-3, 24:3-4.

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[1] I note that in this declaration I am specifically responding to Dr. Albini's opinions with respect to claim construction only. I reserve the right to provide further opinions both with respect to claim construction and to respond to additional statements and opinions set forth in Dr. Albini's declaration if this *inter partes* review is instituted.

40. Dr. Albini states that the preamble language "method for treating" simply means "administering a therapeutic agent to a patient." Ex. 1002, ¶ 43. This, however, ignores the remaining language in the preamble which specifies what is being treated: "an angiogenic eye disorder in a patient." No ordinarily skilled artisan would think that this language encompasses administering the specified treatment to a person suffering, for example, solely from arthritis. Nor would the ordinarily skilled artisan think that the administration of an infinitesimal amount of the specified compound is encompassed by the claim. Neither would constitute a "method for treating an angiogenic eye disorder in a patient." Instead, a skilled artisan would understand the language "[a] method for treating an angiogenic eye disorder in a patient" in the context of the '338 patent to require effectively treating a patient's angiogenic eye condition.

**B. "Tertiary Dose(s)"**

41. Claims 1 and 14 requires that "tertiary dose(s)" are "administered at least 8 weeks after the immediately preceding dose." Ex. 1001 at 23:10-11.

42. It is my opinion that "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."

43. As of the filing date, and even today, the term "tertiary dose(s)" does not have a well-understood meaning to a skilled artisan in the fields of

ophthalmology or retina medicine outside the context of the '338 patent. In my experience, with which Dr. Albini agrees, the term "tertiary dose(s)" is not typically used by clinicians or the skilled artisan. Ex. 1002, ¶ 41.

44. Dr. Albini states that a skilled artisan would understand the term "tertiary dose(s)" as used in the claims of the '338 patent based solely on the following passage from the '338 patent specification:

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

Ex. 1001 at 3:31-45.

45. But in my view, the '338 patent specification provides more context for the meaning of the term "tertiary dose" than the isolated passage above. Indeed, the '338 patent specification explains that, at the time of patent filing in January 2011, therapies for the treatment of angiogenic eye disorders using VEGF antagonists existed in the art. Ex. 1001 at 1:49-52. Nonetheless, the '338 patent recognized that there remained a need for less frequent dosing regimens that could maintain a high

degree of efficacy. *Id.* at 1: 55-59. The '338 patent successfully addressed this long-felt need:

> "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."

*Id.* at 2:3-10 (emphases added).

46. The '338 patent specification makes clear that a key benefit of the claimed dosing regimens is that for "most of the course of treatment (*i.e.* the ***tertiary doses***)" patients may be treated less frequently as compared to therapies that existed in the art (i.e., monthly dosing). *Id.* at 2:15-22 (emphasis added). In my opinion, the disclosed dosing regimens were a significant advance over existing therapies because they enabled physicians, like myself, to treat patients using less frequent dosing, but to maintain a high degree of therapeutic efficacy.

47. I agree with Dr. Albini that the passage at column 3, lines 31-45 quoted above informs the temporal sequence of "initial dose," "secondary dose" and "tertiary dose(s)." I also agree that the "tertiary dose(s)" are third in the sequence of these doses but, in my opinion, this passage does not provide any guidance as to how to determine the appropriate magnitude of the "tertiary dose(s)." However, Patent

Owner's construction captures the full meaning of the term "tertiary dose(s)" in the context of the specification.

48. I also understand that Petitioner argues, and Dr. Albini agrees, that in the context of the '338 patent, "efficacy" "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." Pet. 21; Ex. 1002, ¶ 43. As I read the claims of the '338 patent, in view of the specification, this level of efficacy would not be sufficient for the dosing regimens claimed in the '338 patent. For example, if a patient achieved a letter gain after the initial and secondary doses and then declined after the tertiary dose(s) began, but nonetheless exhibited a loss of fewer than 15 letters during the tertiary dosing, I would not consider this level of efficacy to be sufficient for the dosing regimens claimed in the '338 patent. Rather, I understand "tertiary dose(s)" to require that the efficacy gain achieved from the initial and secondary doses are maintained after the initial and secondary doses. *See, e.g., supra* ¶ 45 (discussing passage in the specification that "[t]he 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."). Thus, the claims as a whole require effective treatment.

49. Consequently, in my opinion, the term "tertiary dose(s)," when viewed from the perspective of a skilled artisan in the context of the specification, means "dose(s), administered after the initial and secondary doses, that maintain(s) the efficacy gain achieved after the initial and secondary doses."

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code.

Dated: August 13, 2021

Diana Do, MD

Diana V. Do, M.D.
Palo Alto, California

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# Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies

*Paul Mitchell, MD, PhD,[1,2,3,4] Ian McAllister, MBBS, DM,[5] Michael Larsen, MD, DMSc,[6,7] Giovanni Staurenghi, MD,[8] Jean-Francois Korobelnik, MD,[9,10] David S. Boyer, MD,[11] Diana V. Do, MD,[12] David M. Brown, MD,[13] Todd A. Katz, MD,[14] Alyson Berliner, MD, PhD,[15] Robert Vitti, MD,[15] Oliver Zeitz, MD,[16,17,18] Carola Metzig, MD,[16] Chengxing Lu, PhD,[14] Frank G. Holz, MD[19]*

***Purpose:*** To evaluate the impact of intravitreal aflibercept (EYLEA, Regeneron Pharmaceuticals, Tarrytown, NY) versus laser on progression of diabetic retinopathy (DR) severity in Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID-DME) and Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema (VISTA-DME).

***Design:*** Secondary and exploratory analyses of 2 phase 3, randomized, controlled studies.

***Participants:*** All patients with a baseline Diabetic Retinopathy Severity Scale (DRSS) score based on fundus photograph (full analysis), patients who progressed to proliferative DR (PDR) (safety analysis) in VIVID-DME (n = 403) and VISTA-DME (n = 459), or both.

***Methods:*** We randomized patients with diabetic macular edema (DME) to intravitreal aflibercept 2 mg every 4 weeks (2q4), intravitreal aflibercept 2 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation at baseline and sham injections at every visit.

***Main Outcome Measures:*** Proportions of patients with 2-step or more and 3-step or more improvements from baseline in DRSS score, who progressed to PDR, and who underwent panretinal photocoagulation (PRP).

***Results:*** Among patients with an assessable baseline DRSS score, most showed moderately severe or severe nonproliferative DR. The proportions of patients treated with 2q4, 2q8, and laser with a 2-step or more improvement in DRSS score at week 100 were 29.3%, 32.6%, and 8.2%, respectively, in VIVID-DME and 37.0%, 37.1%, and 15.6%, respectively, in VISTA-DME; the proportions with a 3-step or more improvement in DRSS score were 7.3%, 2.3%, and 0%, respectively, and 22.7%, 19.9%, and 5.2%, respectively. Fewer patients in the 2q4 and 2q8 groups versus the laser group progressed to PDR at week 100 in VISTA-DME (1.5% and 2.2% vs. 5.3%) and VIVID-DME (3.2% and 2.0% vs. 12.3%). The proportions of patients who underwent PRP were 2.9%, 0.7%, and 4.5%, respectively, in VIVID-DME and 1.9%, 0.7%, and 5.2%, respectively, in VISTA-DME. The most frequent serious ocular adverse event at week 100 was cataract (pooled intravitreal aflibercept, 1.7% of patients; laser, 3.5% of patients).

***Conclusions:*** These analyses demonstrate the benefit of intravitreal aflibercept over laser with respect to DR progression, suggesting a benefit on DME, and on underlying DR. *Ophthalmology Retina 2018;2:988-996 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

*See Editorial on page 985.*

Diabetic retinopathy (DR) is a progressive dysfunction of the retinal vasculature resulting from chronic hyperglycemia.[1] Diabetic retinopathy has been classified into 4 stages: mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). Typical management of mild and moderate NPDR involves observation and improved control of diabetes, whereas severe NPDR and PDR require referral to an ophthalmologist. Treatment options for DR in the absence of diabetic macular edema (DME) target only proliferative stages of DR.

Diabetic macular edema may occur at any point in the course of DR, although it is more frequent as the disease progresses. Most vision loss associated with DR is the result of DME.[2] The estimated global prevalence of DME currently is approximately 21 million,[3] and this is expected to increase with the rising diabetes prevalence; diabetes is projected to affect nearly 600 million people worldwide by 2035.[4]

Intravitreal anti–vascular endothelial growth factor (VEGF) agents (aflibercept [EYLEA, Regeneron Pharmaceuticals, Tarrytown, NY] and ranibizumab) are superior to laser for the treatment of center-involved DME.[5–9] Intravitreal aflibercept showed similar sustainable visual acuity (VA) gains with dosing every other month compared with



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ranibizumab given monthly. More recently, the National Institutes of Health–funded Protocol T study conducted by the Diabetic Retinopathy Clinical Research Network compared intravitreal aflibercept, ranibizumab, and nonlicensed bevacizumab head to head.[10] At 12 months, VA gains achieved with intravitreal aflibercept, the study's primary end point, were statistically superior to those achieved with ranibizumab or bevacizumab, particularly in patients with baseline VA of 20/50 or worse.[10] After 2 years, the visual gains achieved with intravitreal aflibercept were statistically superior to those with bevacizumab, but not ranibizumab[11]; however, an area under the curve analysis showed that mean change in VA over 2 years was greater with intravitreal aflibercept than with bevacizumab or ranibizumab.[12]

Vascular endothelial growth factor inhibition has been shown not only to influence the course of DME positively, but also to have a positive impact on overall DR severity.[6,13,14] Herein we report on an unplanned retrospective analysis of the impact of intravitreal aflibercept treatment on changes in Diabetic Retinopathy Severity Scale (DRSS) scores, progression of DR to PDR in patients with DME, and use of panretinal photocoagulation (PRP) in the Intravitreal Aflibercept Injection in Vision Impairment due to DME (VIVID-DME) and Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema (VISTA-DME) studies.

## Methods

### Design

Study design and methods have been published previously.[8,9] Key details are summarized here. Both VIVID-DME (clinicaltrials.gov identifier, NCT01331681) and VISTA-DME (clinicaltrials.gov identifier, NCT01363440) were phase 3, randomized, double-masked, active-controlled, 148-week trials comparing 2 dosing regimens of intravitreal aflibercept with laser for the treatment of DME. The studies were conducted at 127 sites in the Unites States, Europe, Japan, and Australia and in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation. All information presented in this study complies with the Health Insurance Portability and Accountability Act for United States sites. Institutional review board or ethics committee approval was obtained at each site before the studies commenced, and all patients provided written consent.

### Participants

Adult patients with diabetes mellitus with central DME involvement (defined as retinal thickening involving the 1-mm central OCT subfield [central subfield thickness]) were included if best-corrected VA (BCVA) was between 73 and 24 letters (Snellen equivalent, 20/40–20/320) in the study eye. Only 1 eye per patient was included.

### Randomization and Treatment

We randomized patients 1:1:1 to treatment with intravitreal aflibercept 2.0 mg every 4 weeks (2q4), intravitreal aflibercept 2.0 mg every 8 weeks after 5 initial monthly doses (2q8), or macular laser photocoagulation at baseline and sham injections at every visit. Eyes in the 2q8 group received sham injections on nontreatment visits. From week 24 onward, additional active treatment (laser in the intravitreal aflibercept groups or intravitreal aflibercept in the laser group) was allowed if BCVA decreased because of disease reoccurrence or worsening based on prespecified criteria. Panretinal photocoagulation was allowed at any time at the investigator's discretion for PDR.

### Outcomes

The primary efficacy end point in VIVID-DME and VISTA-DME was the BCVA change from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores at week 52. Results for the primary end point of these studies are reported elsewhere.[8] Herein, we report the proportion of eyes with 2-step or more and 3-step or more improvement in DRSS score at weeks 52 and 100, the proportion of eyes in which PDR developed at weeks 52 and 100, and the proportion of eyes that underwent PRP at weeks 52 and 100. The 2-step or more improvement in DRSS score was a prespecified secondary end point at week 52 and an exploratory end point at week 100 for these studies.

We assessed central subfield thickening using spectral-domain OCT every 4 weeks, and performed fluorescein angiography and color fundus photography at baseline and weeks 24, 52, and 100. Masked graders evaluated images at independent reading centers. For VIVID-DME, readers at the Vienna Reading Center (Vienna, Austria) evaluated OCT images and fundus images. For VISTA-DME, clinicians at the Duke Reading Center (Durham, NC) assessed OCT images and clinicians at the Digital Angiography Reading Center (Great Neck, NY) evaluated fundus images. Although the 2 reading centers used similar methods, the differences in the proportions of ungradable images at baseline were the result of slightly different algorithms used by each center.

Patients were considered to have PDR if their baseline DRSS score was less than 61 and there was at least 1 postbaseline DRSS score of 61 or more. Laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1 and active PDR in the study eye were exclusion criteria for VIVID-DME and VISTA-DME. Approximately 5% of patients demonstrated PDR at baseline. It was agreed by the reading centers that DRSS level 60 (which indicates prior PRP) would not be used in the study, and therefore patients with prior PRP could still improve on the DRSS scale.

### Statistical Analysis

Patients included in the efficacy analyses are those from the full analysis set (FAS) in both studies (VIVID-DME and VISTA-DME). This includes all randomized patients who received any study medication and underwent at least 1 baseline and 1 postbaseline assessment. We analyzed the FAS as randomized. In calculating the percentage of patients with a 2-step or more and 3-step or more improvement in DRSS score, the denominator for VIVID-DME was all patients in the FAS who had a baseline evaluable measurement of DRSS score and at least 1 postbaseline evaluable assessment of DRSS score; the denominator for VISTA-DME was all patients in the FAS. For patients missing a DRSS score at weeks 52 and 100, we imputed missing values using the last observation carried forward method, in which we used the last value before additional treatment for eyes that received additional treatment. The use of these different denominators is consistent with the health authority submission packages for the 2 studies. For the end point of PDR development, we excluded missing and ungradable entries for DRSS score from both studies.

We calculated results for all end points for each treatment group (2q4, 2q8, and laser) for VIVID-DME and VISTA-DME. Additionally, given the low number of cases of incident PDR, we integrated the populations from both studies and calculated the end points for 2 groups from that integrated population: a pooled intravitreal aflibercept group (2q4 and 2q8) and laser group. In the case of the integrated and pooled results, we based $P$ values on the Fisher exact test without further adjusting for multiplicities. Patients included in safety analyses are from the safety population in both studies, which includes all randomized patients who received any study treatment.

## Results

### Changes from Baseline in Diabetic Retinopathy Severity Scale Scores

Of 862 patients in the FAS, 748 (86.8%) had a baseline DRSS score (Table 1). The proportions of DRSS images categorized as ungradable were 25%, 28.7%, and 25.2% for the Vienna Reading Center and 2.6%, 0.6%, and 2.0% for the Digital Angiography Reading Center for the laser, 2q4, and 2q8 groups, respectively.

A greater proportion of patients treated with intravitreal aflibercept (both 2q4 and 2q8) in both VIVID-DME and VISTA-DME demonstrated a 2-step or more improvement in DRSS scores at weeks 52 and 100 compared with laser-treated patients (Fig 1). When the data from the studies were integrated, the proportion of patients who showed a 2-step or more improvement was greater in the pooled intravitreal aflibercept group compared with the laser group (week 52: 31.1% vs. 12.0%, $P < 0.0001$; week 100: 34.9% vs. 13.0%, $P < 0.0001$; n = 578 and 287, respectively, for both time points).

The proportion of patients with a 3-step or more improvement in DRSS score at weeks 52 and 100 was greater among the groups treated with intravitreal aflibercept 2q4 and 2q8 than among those treated with laser (Fig 2). When the data from the studies were integrated, the proportion of patients who showed a 3-step or more improvement was greater in the pooled intravitreal aflibercept group compared with the laser group (week 52: 10.7% vs. 3.4%, $P = 0.0008$; week 100: 15.4% vs. 3.3%, $P < 0.0001$; n = 578 and 287, respectively, for both time points). Figure 3 shows a representative example of a fundus photograph from a patient treated with intravitreal aflibercept who experienced a 2-step or more improvement in DRSS score at week 52.

### Progression to Proliferative Diabetic Retinopathy

A smaller proportion of patients in the intravitreal aflibercept 2q4 and 2q8 groups demonstrated PDR through weeks 52 and 100 compared with patients in the laser group (Fig 4). When the data from the studies were integrated, the proportion of patients in whom PDR developed was smaller in the pooled intravitreal aflibercept group compared with the laser group (week 52: 1.7% vs. 7.0%, $P = 0.0002$; week 100: 2.2% vs. 9.1%, $P \leq 0.0001$; n = 578 and 287, respectively, for both time points).

Finally, the proportion of patients treated with intravitreal aflibercept 2q4 and 2q8 versus laser who received PRP through weeks 52 and 100 was smaller than the proportion of laser-treated patients who received PRP (Fig 5). When we integrated the data from the studies, the proportion of patients who received PRP developed was smaller in the pooled intravitreal aflibercept group compared with the laser group (week 52: 0.9% vs. 3.5%, $P = 0.0099$; week 100: 1.6% vs. 4.9%, $P = 0.0064$; n = 578 and 287, respectively, for both time points). Not all cases of PDR led to

Table 1. Baseline Diabetic Retinopathy Severity Scale Scores in VIVID-DME and VISTA-DME

| | | VIVID-DME | | | VISTA-DME | | |
|---|---|---|---|---|---|---|---|
| | Diabetic Retinopathy Severity Scale Score | *Laser (n = 132)* | *Intravitreal Aflibercept 2 mg Every 4 Weeks (n = 136)* | *Intravitreal Aflibercept 2 mg Every 8 Weeks after 5 Initial Monthly Doses (n = 135)* | *Laser (n = 154)* | *Intravitreal Aflibercept 2 mg Every 4 Weeks (n = 154)* | *Intravitreal Aflibercept 2 mg Every 8 Weeks after 5 Initial Monthly Doses (n = 151)* |
| None | 10 | 0 | 0 | 0 | 1 (0.6) | 4 (2.6) | 4 (2.6) |
| Mild to moderate NPDR | 20 | 1 (0.8) | 0 | 0 | 3 (1.9) | 5 (3.2) | 3 (2.0) |
| | 35 | 2 (1.5) | 0 | 1 (0.7) | 5 (3.2) | 7 (4.5) | 9 (6.0) |
| | 43 | 36 (27.3) | 31 (22.8) | 28 (20.7) | 60 (39.0) | 49 (31.8) | 52 (34.4) |
| Moderately severe/severe NPDR | 47 | 24 (18.2) | 18 (13.2) | 27 (20.0) | 26 (16.9) | 26 (16.9) | 32 (21.2) |
| | 53 | 35 (26.5) | 44 (32.4) | 42 (31.1) | 42 (27.3) | 53 (34.4) | 40 (26.5) |
| Mild/moderate/high-risk/ advanced PDR | 61 | 1 (0.8) | 2 (1.5) | 2 (1.5) | 1 (0.6) | 1 (0.6) | 2 (1.3) |
| | 65 | 0 | 2 (1.5) | 1 (0.7) | 10 (6.5) | 4 (2.6) | 5 (3.3) |
| | 71 | 0 | 0 | 0 | 1 (0.6) | 4 (2.6) | 1 (0.7) |
| | 75 | 0 | 0 | 0 | 1 (0.6) | 0 | 0 |
| Cannot grade | 90 | 33 (25) | 39 (28.7) | 34 (25.2) | 4 (2.6) | 1 (0.6) | 3 (2.0) |

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VISTA-DME = Intravitreal Aflibercept Injection in Vision Impairment due to DME; VIVID-DME = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema.
Full analysis set. Data are no. (%).

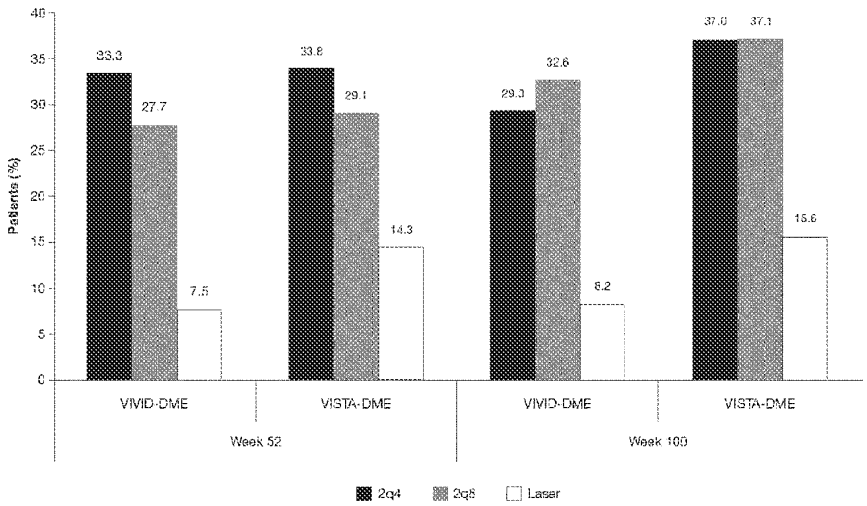


**Figure 1.** Bar graph showing the proportion of patients with 2-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score. For analysis of DRSS, all patients in the full analysis set (FAS) who had a baseline evaluable measurement of DRSS score and at least 1 postbaseline evaluable assessment of DRSS score were included. VIVID-DME: laser, n = 132; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 154; 2q8, n = 151.

PRP; it is possible that PRP was administered at time points other than the DRSS reading time points, leading to the different proportions seen in Figures 4 and 5.

## Safety

The incidence of adverse events related to the progression of DR was low. The proportions of patients who underwent vitrectomy in the laser, intravitreal aflibercept 2q4, and intravitreal aflibercept 2q8 treatment groups were 0%, 0.7%, and 0%, respectively, in VIVID-DME and 0.6%, 1.9%, and 0.7%, respectively, in VISTA-DME. The proportions of patients in the laser, intravitreal aflibercept 2q4, and intravitreal aflibercept 2q8 treatment groups in whom vitreous hemorrhage developed through week 100 were 4.5%, 2.9%, and 3.0%, respectively, in VIVID-DME and 9.1%, 6.5%, and 2.0%, respectively, in VISTA-DME.

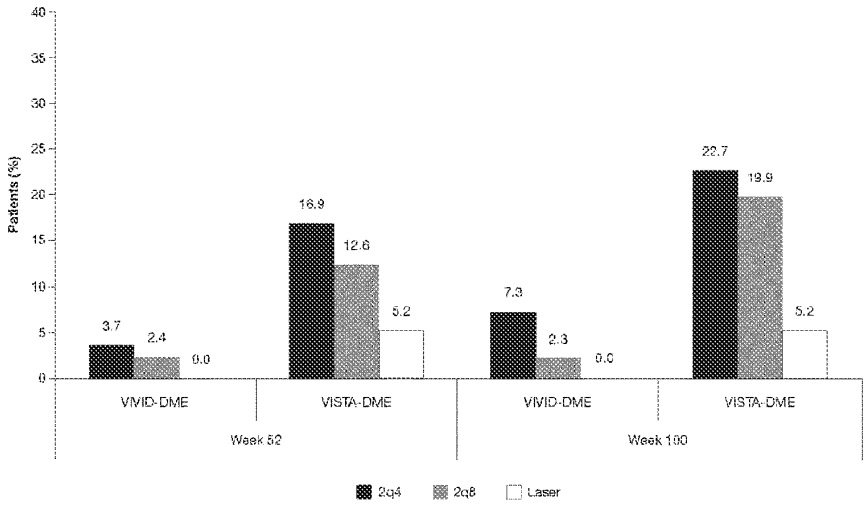


**Figure 2.** Bar graph showing the proportion of patients with 3-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score. For analysis of DRSS, all patients in the full analysis set (FAS) who had a baseline evaluable measurement of DRSS score and at least 1 postbaseline evaluable assessment of DRSS score were included. VIVID-DME: laser, n = 132; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 154; 2q8, n = 151.

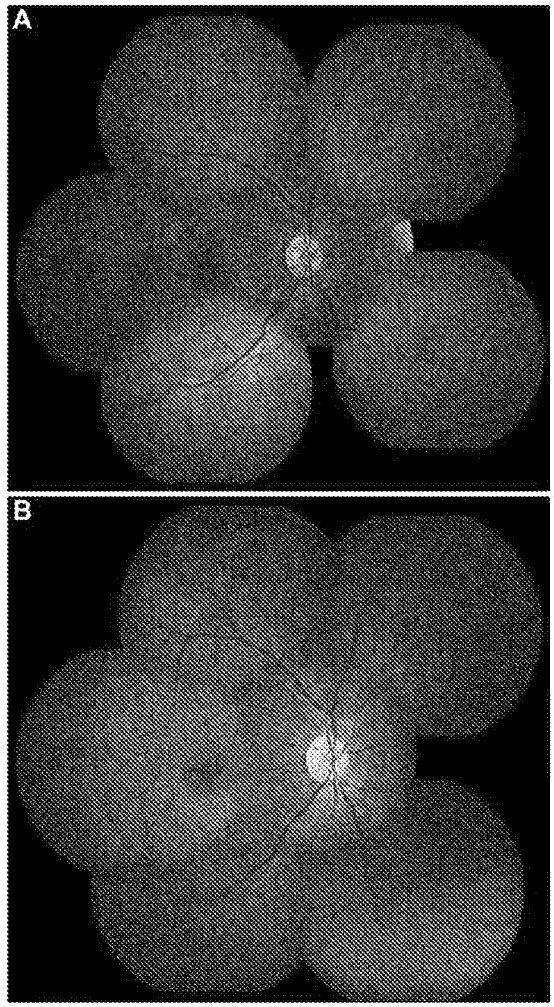


Figure 3. Representative examples of fundus photographs from an intravitreal aflibercept-treated patient from VIVID-DME who experienced a 2-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score (A) at baseline and (B) at week 52.

## Discussion

These analyses evaluated the impact of intravitreal aflibercept on DR in patients with DME enrolled in the VIVID-DME and VISTA-DME trials. Compared with laser, the proportion of patients in the intravitreal aflibercept groups who achieved a 2-step or more and 3-step or more improvement in DRSS score was greater, and the proportion of patients in whom PDR developed, who were treated with PRP, or both was smaller. These results were seen in both the 2q4 and 2q8 treatment groups, suggesting that a reduced number of intravitreal aflibercept injections does not decrease the treatment benefit provided.

The Diabetic Retinopathy Clinical Research Network Protocol S study demonstrated that, in eyes with PDR, ranibizumab 0.5 mg administered as needed was noninferior to PRP with respect to BCVA outcomes at 2 years, and the cumulative benefit of ranibizumab over the study period was superior to PRP.[15] In the Clinical Efficacy of Intravitreal Aflibercept versus Panretinal Photocoagulation for Best Corrected Visual Acuity in Patients with Proliferative Diabetic Retinopathy at 52 weeks (CLARITY) study, intravitreal aflibercept administered as needed (after 3 initial monthly doses) was noninferior and superior to PRP in terms of mean change in BCVA at 52 weeks.[16] The Diabetic Anti-VEGF study compared ranibizumab 0.3-mg monotherapy with combination ranibizumab plus targeted retinal photocoagulation and found no differences between groups in visual improvement or decreases in central retinal thickness (Brown DM et al. Unpublished observations, 2015). These studies suggest a beneficial effect of anti-VEGF on the underlying diffuse DR in eyes with DME, which also was seen in the current analyses.

The VIVID-DME and VISTA-DME trials were the first anti-VEGF studies to examine the improvement of DR as a prespecified end point; however, progression of DR has been evaluated in other studies. The A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE) and A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE) studies found a trend similar to those seen in VIVID-DME and VISTA-DME, with a greater proportion of ranibizumab-treated patients experiencing a 2-step or more or 3-step or more improvement in DRSS score compared with sham-treated patients and a smaller proportion in whom PDR developed or who underwent PRP.[17] However, the results in RISE and RIDE were achieved with monthly injections of ranibizumab (median of 24 injections over 2 years),[5] whereas in the 2q8 group of VIVID-DME and VISTA-DME, the total number of injections received from baseline to week 100 was lower (mean, 13.5 injections in VISTA and 13.6 injections in VIVID over 2 years[9]). Additionally, the distribution of baseline DRSS scores was different in RISE and RIDE compared with VIVID-DME and VISTA-DME. In RISE and RIDE, the distribution of patients with mild to moderate NPDR, moderately severe to severe NPDR, and PDR was roughly equal (approximately one third of patients in each group).[17] In VIVID-DME and VISTA-DME, nearly half of patients demonstrated moderately severe to severe NPDR at baseline, and less than 10% demonstrated PDR (Table 1).

The Diabetic Retinopathy Clinical Research Network conducted an exploratory analysis of the Protocol I study to evaluate the effects of intravitreal ranibizumab or triamcinolone on the progression of DR, which was defined as (1) worsening from no PDR to PDR, (2) worsening of 2 or more severity levels on reading center assessment of fundus photographs in eyes without PDR at baseline, (3) having PRP, (4) having vitreous hemorrhage, or (5) requiring vitrectomy for treatment of PDR. Intravitreal ranibizumab was associated with a reduced risk of DR worsening in eyes with

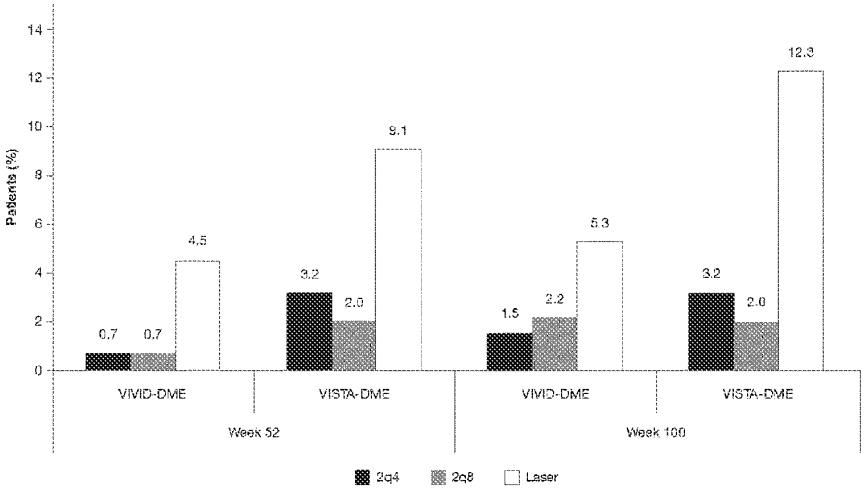


**Figure 4.** Bar graph showing the proportion of patients in whom proliferative diabetic retinopathy (PDR) developed, safety analysis set. For both studies, PDR development was defined as patients with baseline Diabetic Retinopathy Severity Scale (DRSS) value of less than 61 and at least 1 postbaseline DRSS value of 61 or more. VIVID-DME: laser, n = 133; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 155; 2q8, n = 152.

or without PDR, and intravitreal triamcinolone was associated with a reduced risk of PDR worsening.[18]

A post hoc analysis of the Protocol T study evaluated the proportion of patients with DR improvement at 1 and 2 years and the cumulative probabilities for DR worsening through 2 years without adjustment for multiple outcomes. In eyes with NPDR at baseline, anti-VEGF treatment resulted in improvement in DR severity for 22.1% to 37.7% at year 1 and 22.1% to 31.0% at year 2; less improvement was observed with bevacizumab compared with intravitreal aflibercept or ranibizumab. Among eyes with PDR at baseline, intravitreal aflibercept was associated with more DR improvement at 1 and 2 years. Use of all 3 anti-VEGF agents was associated with low rates of DR worsening.[14]

In the ETDRS, 1 eye of each patient was assigned to early photocoagulation, whereas the other was assigned to

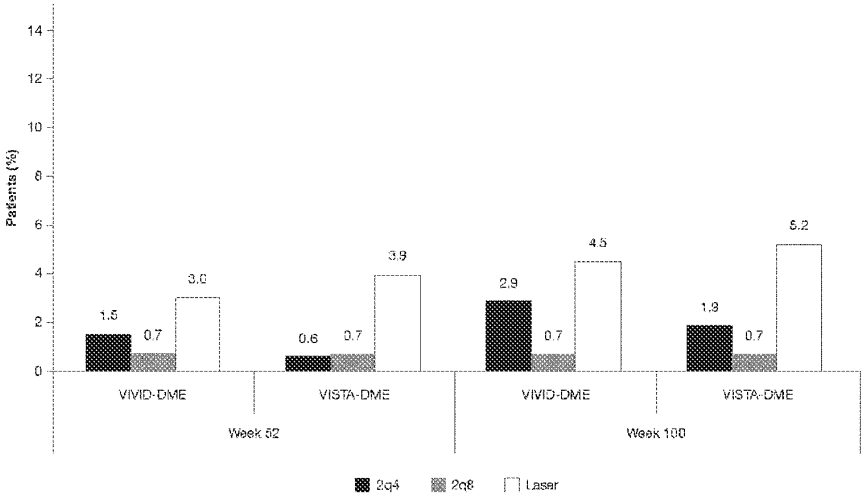


**Figure 5.** Bar graph showing the proportion of patients who underwent panretinal laser photocoagulation, safety analysis set. VIVID-DME: laser, n = 133; 2 mg every 4 weeks (2q4), n = 136; 2 mg every 8 weeks after 5 initial monthly doses (2q8), n = 135; VISTA-DME: laser, n = 154; 2q4, n = 155; 2q8, n = 152.

deferred photocoagulation, allowing observation of the natural course of DR in the initially untreated eye. The proportions of eyes with progression to PDR were 22.8%, 40.2%, and 54.7%, at 1, 3, and 5 years of follow-up, respectively.[19] These proportions are substantially higher than the proportions of patients in whom PDR developed, who underwent PRP, or both in any of the treatment groups of VIVID-DME and VISTA-DME. The lower rates seen in the current studies may be the result of temporal improvements in glycemic control made possible by advances in diabetes treatment over the last 25 years, shown to reduce progression of DR.[20–24] Mean baseline hemoglobin A1c levels for patients in VIVID-DME and VISTA-DME ranged from 7.6% to 7.9% and did not change over the course of the study; in contrast, 42.0% of patients enrolled in the ETDRS before 1983 had a baseline hemoglobin A1c of 10% or more.[25]

The current analysis has some limitations. The relative infrequency of DRSS measurements (at baseline, weeks 24, 52, 72 [VISTA-DME] or 76 [VIVID-DME], and 100) means that it is possible that there are patients in any treatment group who did progress to PDR, but that this resolved spontaneously during continued treatment and was not captured. Additionally, investigators administered PRP at their discretion, a clinical decision that likely was driven by multiple factors. There was no specific guidance indicating when PRP should be performed, and therefore some investigators may have chosen to wait for high-risk PDR to develop. Others may have deferred PRP because of the expectation of a positive treatment effect on the condition. Finally, images for the 2 studies were graded by 2 different reading centers. The reading centers used different criteria to grade images; however, both approaches are considered valid per the ETDRS DRSS protocol. The overall similarity of the results between the 2 studies suggests that the different grading criteria did not impact the outcomes.

In conclusion, these analyses through week 100 demonstrated the benefits of intravitreal aflibercept over laser in terms of DR progression, improvement, and outcomes, suggesting that intravitreal aflibercept has a beneficial impact not only on localized DME, but also on the underlying DR.

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A.B.: Employee and Equity owner — Regeneron Pharmaceuticals, Inc

R.V.: Employee and Equity owner — Regeneron Pharmaceuticals, Inc

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HUMAN SUBJECTS: Human subjects were included in this study. The studies were conducted at 127 sites in the United States, Europe, Japan, and Australia. Institutional review board or ethics committee approval was obtained at each site. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Mitchell, McAllister, Larsen, Staurenghi, Korobelnik, Boyer, Do, Brown, Katz, Berliner, Vitti, Zeitz, Metzig, Holz

Analysis and interpretation: Mitchell, McAllister, Larsen, Staurenghi, Korobelnik, Boyer, Do, Brown, Katz, Berliner, Vitti, Zeitz, Metzig, Lu, Holz

Data collection: Mitchell, McAllister, Larsen, Staurenghi, Korobelnik, Boyer, Do, Brown

Obtained funding: N/A

Overall responsibility: Mitchell, McAllister, Larsen, Staurenghi, Korobelnik, Boyer, Do, Brown, Katz, Berliner, Vitti, Zeitz, Metzig, Lu

Abbreviations and Acronyms:
**BCVA** = best-corrected visual acuity; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FAS** = full analysis set; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **PRP** = panretinal photocoagulation; **RIDE** = A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus; **RISE** = A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VISTA-DME** = Study of Intravitreal Aflibercept Injection in Patients with Diabetic Macular Edema; **VIVID-DME** = Intravitreal Aflibercept Injection in Vision Impairment due to DME; **2q4** = 2 mg every 4 weeks; **2q8** = 2 mg every 8 weeks after 5 initial monthly doses.

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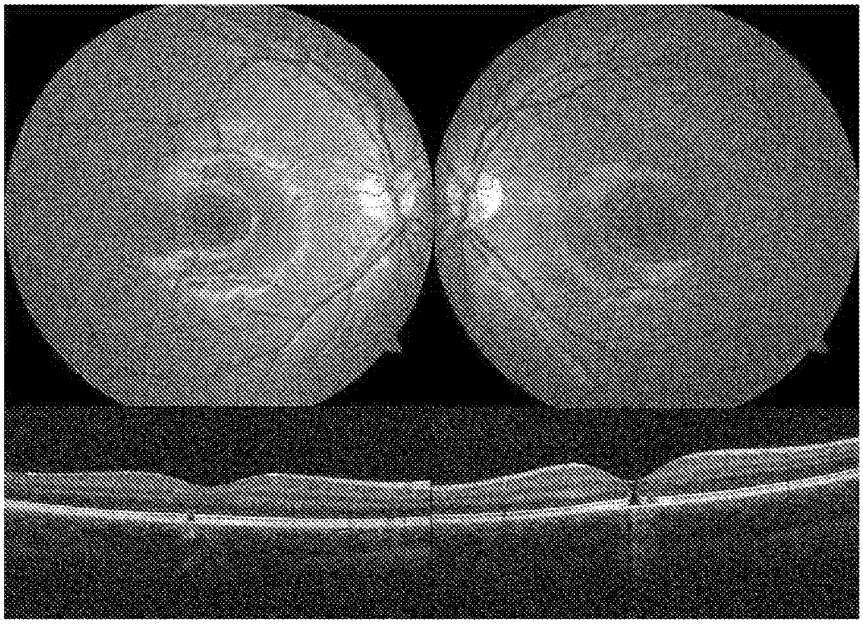
## Pictures & Perspectives



**Laser Pointer Maculopathy**

An 11-year old Caucasian boy was referred for loss of vision for 1 year concerning for inherited retinal dystrophy. Best-corrected visual acuity was 20/30 in the right eye and 20/80 in the left. No family history of early vision loss was noted. Anterior segment examination was unremarkable. Dilated fundus examination showed irregular areas of foveal atrophy in both eyes. OCT shows a focal, well-circumscribed area of photoreceptor loss subfoveally in the left eye and parafoveally in the right eye. Upon further questioning, he admits that before noticing the vision changes a friend had shined a laser pointer in his eyes for a prolonged period of time.

Laura Snyder, MD
Shrija Patel, MD

*Vanderbilt Eye Institute, Nashville, Tennessee*

# Prevention of Experimental Choroidal Neovascularization and Resolution of Active Lesions by VEGF Trap in Nonhuman Primates

*T. Michael Nork, MD, MS; Richard R. Dubielzig, DVM; Brian J. Christian, PhD; Paul E. Miller, DVM; Jacqueline M. Miller, BS; Jingtai Cao, MD, PhD; Edward P. Zimmer, PhD; Stanley J. Wiegand, PhD*

**Objective:** To evaluate the efficacy of systemic and intravitreous administration of VEGF Trap (aflibercept) in a nonhuman primate model of choroidal neovascularization (CNV).

**Methods:** VEGF Trap treatment on laser-induced CNV was evaluated in 48 adult cynomolgus monkeys. In the prevention arms of the study, VEGF Trap was administered by intravenous injection (3 or 10 mg/kg weekly) or intravitreous injection (50, 250, or 500 µg/eye every 2 weeks) beginning before laser injury. In the treatment arm, a single intravitreous injection (500 µg) was given 2 weeks following laser injury. Laser-induced lesions were scored from grade 1 (no hyperfluorescence) to grade 4 (clinically relevant leakage). Representative lesions were evaluated histologically.

**Results:** Grade 4 leakage developed at 32.4% and 45.4% of the laser sites in animals receiving intravitreous or intravenous administration of placebo at 2 weeks following laser injury, respectively. In contrast, the development of grade 4 lesions was completely or nearly completely prevented in all groups receiving intravenous or intravitreous injections of VEGF Trap. A single intravitreous injection of VEGF Trap (500 µg) administered following the development of CNV reduced the frequency of grade 4 lesions from 44.4% to 0% within 14 days of treatment. Intravitreous VEGF Trap was well tolerated with either no or only mild ocular inflammation. Histological evaluation showed decreased scores for morphologic features of tissue proliferation in the VEGF Trap prevention groups.

**Conclusions:** VEGF Trap prevented the development of clinically relevant CNV leakage when administered at the lowest doses tested. Moreover, a single intravitreous injection induced inhibition of active CNV leakage.

**Clinical Relevance:** The animal model used in this study has an established track record as a predictor of pharmacologic efficacy of antineovascular drugs in humans having the neovascular, or wet, form of age-related macular degeneration.

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**Author Affiliations:** Comparative Ophthalmic Research Laboratories (CORL) (Drs Nork, Dubielzig, and P. E. Miller) and Covance Laboratories, Inc (Dr Christian and Ms J. M. Miller), Madison, Wisconsin; and Regeneron Pharmaceuticals, Inc, Tarrytown, New York (Drs Cao, Zimmer, and Wiegand).

AGE-RELATED MACULAR DEgeneration (AMD) is a leading cause of blindness whose incidence is likely to increase as the population ages.[1] The great majority of individuals with AMD have the dry form, which is characterized by atrophic degeneration of the retinal pigment epithelium with secondary (and often gradual) damage to the photoreceptors. However, 80% to 90% of patients with AMD who develop severe vision loss have the wet (neovascular) form,[2] which occurs when abnormal new blood vessels originating from the choroid grow through the Bruch membrane into the subretinal or intraretinal space. This choroidal neovascularization (CNV) was formerly treated with thermal laser photocoagulation according to protocols developed as part of the Macular Photocoagulation Study and related subsequent studies.[3-8] Although the treatment was effective at slowing the progression of the disease, it seldom resulted in improved vision because the thermal laser also irreversibly damaged the overlying retina. The patients were often left with central scotomas from the treatment itself. Since then, drugs such as pegaptanib sodium (Macugen) and ranibizumab (Lucentis) have been developed for human use; these work by inhibiting vascular endothelial growth factor (VEGF).

VEGF Trap is a potent VEGF inhibitor comprising ligand-binding portions of human VEGF receptor 1 (VEGFR1) and VEGFR2 fused to the Fc segment of human IgG1 (**Figure 1**).[9] VEGF Trap binds and neutralizes multiple isoforms of

VEGF-A (dissociation constant of approximately 1pM) as well as the related angiogenic factor placental growth factor (PlGF) (dissociation constant of approximately 40pM). An intravenous formulation of VEGF Trap, generically known as aflibercept, is being developed for oncology; this formulation is hyperosmotic and diluted prior to intravenous infusion. VEGF Trap-Eye, known generically as aflibercept ophthalmic solution, is an isoosmotic, ultrapurified formulation of VEGF Trap for intravitreous injection. Phase 3 studies of VEGF Trap-Eye in patients with neovascular AMD and retinal vein occlusion are currently in progress.

The purposes of this study were to evaluate the efficacy of systemic and intravitreous administration of VEGF Trap in a primate model of CNV and to evaluate histological changes associated with the angiographic improvements observed. This study was completed prior to initiating the human clinical trial program for VEGF Trap-Eye.

## METHODS

### LASER INDUCTION OF CNV

The effect of VEGF Trap treatment on laser-induced CNV was evaluated in cynomolgus monkeys (1.8-2.7 kg at initiation of dosing) using a modification[10] of a model of CNV developed by Ryan[11] and Ohkuma and Ryan.[12] All of the experimental methods and techniques adhered to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by our institutional animal care and use committee. Animals were anesthetized with ketamine hydrochloride and xylazine hydrochloride. A 532-nm diode laser (OcuLight GL; Iridex Corp, Mountain View, California) with a table-mounted slitlamp adapter was used to create small (75-μm diameter), intense laser spots of 0.1-second duration that were applied to 9 areas of the macula of each eye. Initially, the power setting was 500 mW for all spots except the one just temporal to the fovea, which was treated with 400 mW. If no hemorrhage occurred at a given spot, a second spot was placed adjacent to it using a laser intensity of 150 mW greater than the initial burn. The development of active CNV lesions was assessed by fluorescein angiography (FA), once before injury and 15, 20, and 29 days after laser injury. The CNV lesions were graded by a masked observer (T.M.N.) using the following scale: grade 1, no hyperfluorescence; grade 2, hyperfluorescence, without leakage; grade 3, hyperfluorescence early or midtransit, and late leakage; and grade 4, bright hyperfluorescence early or midtransit, with late leakage extending beyond the borders of the laser spot.

### TREATMENT PARADIGMS

In the prevention studies, VEGF Trap was administered by intravenous injection (3 or 10 mg/kg of body weight weekly) or intravitreous injection (50, 250, or 500 μg/eye every 2 weeks) beginning approximately 1 week before laser injury. For intravitreous injection, VEGF Trap was formulated in 10mM sodium phosphate, 135mM sodium chloride, and 0.1% polyethylene glycol 3350 (pH 6.25) and injected through a 30-gauge sterile needle in a volume of 50 μL (500 or 50 μg) using a 1-mL tuberculin syringe or 25 μL (250 μg) using a 0.3-mL syringe. VEGF Trap for intravenous injection was formulated in 5mM sodium phosphate, 5mM sodium citrate, 100mM sodium chloride, 20% sucrose, and 0.1% polysorbate 20 (pH 6.0) and infused in a volume of 4 to 5 mL/kg of body weight over 30 minutes. Control animals received weekly intravenous infusions or biweekly intravitreous injections (50 μL) of placebo comprising the appropriate vehicle solutions according to the same schedule as for corresponding VEGF Trap–treated groups.

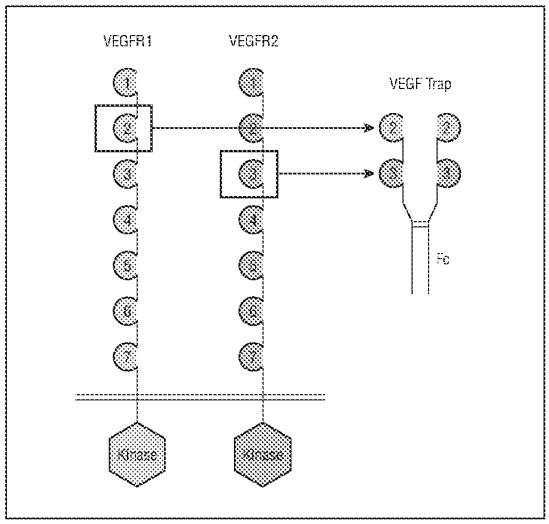


**Figure 1.** VEGF Trap is a fusion protein comprising the ligand-binding domains 2 and 3 of human vascular endothelial growth factor receptors 1 and 2 (VEGFR1 and VEGFR2), respectively, attached to the Fc portion of human IgG1. Recombinant VEGF Trap is produced in Chinese hamster ovary cells, has a protein molecular weight of 97 kDa, and is approximately 15% glycosylated to yield a total molecular weight of 115 kDa.

In the treatment study, a single intravitreous injection of VEGF Trap (500 μg) was given 15 days following laser injury, at which time active CNV had already formed. Each of the experimental and control groups comprised 6 animals, including 3 males and 3 females; both eyes were treated identically (**Table 1**).

### INTRAVITREOUS INJECTIONS

Animals were anesthetized with ketamine and xylazine, and the eyes were instilled with 0.5% proparacaine hydrochloride, cleaned with 2.5% povidone-iodine, and rinsed with sterile saline. Immediately following each injection, a single topical dose of tobramycin and dexamethasone (Tobradex) ointment was applied to the eye. No systemic antibiotics were used. The left and right eyes of each animal received the same dose of either VEGF Trap or placebo (as opposed to a study design that used the fellow eye as the control) to eliminate the possibility of a systemic effect on the control eye.

### OPHTHALMIC EXAMINATIONS

Daily cage-side observations were performed on all animals to monitor for clinical signs of poor health, including any ocular abnormalities. Animals also underwent clinical ophthalmic examinations before the initiation of treatment and on postlaser days 7, 21, and 32 (intravitreous prevention groups) and days 9, 23, and 33 (intravenous prevention groups and intravitreous treatment group, excluding day 9). The anterior portion of each eye was viewed using a handheld slitlamp biomicroscope, and the ocular fundus was viewed with an indirect ophthalmoscope. Intraocular pressure was monitored. Fundus photographs were taken on the day of laser treatment (following laser injury) and approximately 4 weeks later, preceding the final FA.

**Table 1. Group Designation and Dose Levels**

| Group[a] | Animals, No. Male | Animals, No. Female | Dose Volume | Dose Concentration, mg/mL |
|---|---|---|---|---|
| Intravenous prevention | | | | |
| Placebo | 3 | 3 | 4.78 mL/kg | 0 |
| 3 mg/kg/dose | 3 | 3 | 4.35 mL/kg | 0.69 |
| 10 mg/kg/dose | 3 | 3 | 4.78 mL/kg | 2.09 |
| Intravitreous prevention | | | | |
| Placebo | 3 | 3 | 0.05 mL/eye | 0 |
| 50 µg/eye/dose | 3 | 3 | 0.05 mL/eye | 1 |
| 250 µg/eye/dose | 3 | 3 | 0.025 mL/eye | 10 |
| 500 µg/eye/dose | 3 | 3 | 0.05 mL/eye | 10 |
| Intravitreous treatment | | | | |
| Single dose of 500 µg/eye | 3 | 3 | 0.05 mL/eye | 10 |

[a]Animals in the 2 control groups (intravenous and intravitreous) were administered a placebo vehicle following the same regimens as treated animals in the intravenous and intravitreous VEGF Trap treatment arms. In the prevention studies, intravenous doses were administered weekly for a total of 6 doses, and intravitreous doses were administered every other week for a total of 3 doses, beginning approximately 1 week before laser injury. In the treatment study, animals received a single dose of VEGF Trap following the establishment of active grade 4 lesions, 15 days following laser injury. See Figure 2 for the dosing schedule.

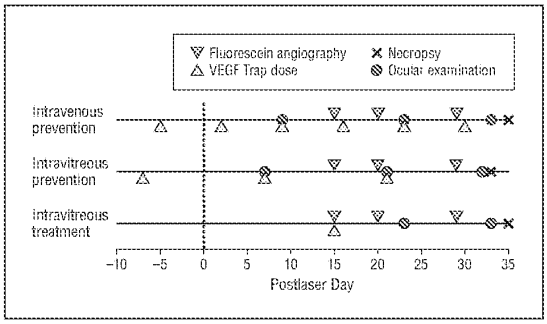


**Figure 2.** Timeline for dosing, ocular examinations, and fluorescein angiography relative to laser photocoagulation.

Anterior chamber and vitreous cell scores were determined for right and left eyes using a slitlamp biomicroscope as follows: a score of 0 indicates no cells observed; a score of 0.5+, 1 to 5 cells per single field of focused beam; a score of 1+, 5 to 25 cells per single field of focused beam; a score of 2+, 25 to 50 cells per single field of focused beam; a score of 3+, 50 to 100 cells per single field of focused beam; and a score of 4+, more than 100 cells per single field of focused beam. Scores from both eyes were averaged per animal. Means and standard deviations are based on 6 animals per group. **Figure 2** shows the timing of dosing, FA, ophthalmic examinations, and necropsy relative to the day of laser treatment for each of the 3 treatment arms.

## STATISTICAL ANALYSIS OF LASER LESION GRADES

For each of the 3 postlaser angiography intervals (days 15, 20, and 29), the proportions of grade 4 counts were dichotomized to 1 and 0 and the Cochran-Armitage trend test was applied to the intravenous prevention and intravitreous prevention groups separately. Fisher exact tests were also conducted for group comparisons between treated groups and the control group.

For the intravitreous treatment group and the intravitreous prevention placebo group, data from day 15 were treated as baseline data and were subtracted from the data on days 20 and 29. The difference was then analyzed for days 20 and 29 separately using Wilcoxon signed rank test.

All test results are exact because of the small sample sizes. All statistical tests were conducted at the 5% level.

## HISTOLOGICAL ASSESSMENT OF CNV LESIONS

Animals were killed on postlaser day 33 (intravitreous prevention groups) or day 35 (intravenous prevention groups and intravitreous treatment group) and the upper body was perfused through the aorta (descending clamped) with half-strength Karnovsky fixative. The eyes were removed, post-fixed for 2 to 3 days in half-strength Karnovsky fixative, and then stored in formalin until processed.

One eye from each animal in the intravitreous placebo, VEGF Trap (500 µg) prevention, and VEGF Trap treatment groups was selected for histopathological evaluation. The selected eyes were representative and comprised approximately half of the grade 4 lesions for each of the groups. Strips of tissue containing 1 or 2 lesion sites were embedded in plastic. Sections 2 µm thick were taken at 30-µm steps through the middle of each lesion. The sections were stained with toluidine blue, and the sample with the most robust lesion was designated as the central cut. This section was then evaluated by an observer (R.R.D.) masked to the treatment condition.

A tissue proliferation score was calculated for each lesion based on 3 criteria: the size of the spindle cell proliferative lesion, the extent of new blood vessel proliferation in the subretinal space, and the elevation of the retina above the choriocapillaris (**Figure 3**). Each measure was graded from 0 to 3, with 0 indicating not present. The total tissue proliferation score comprises the sum of each of the described measures for each laser lesion site.

# RESULTS

## INFLAMMATORY RESPONSE

Intravitreous administration of the VEGF Trap placebo control article was well tolerated, with 0.5+ vitreous cells seen in 1 of 6 animals in this group. No anterior chamber cells were detected at the designated examination times in animals receiving intravitreous injections of placebo (**Table 2**).

Intravitreous administration of the VEGF Trap test material at all dose levels resulted in no (0) or mild (0.5+ to 1+) inflammatory cell scores in the anterior chamber or vitreous. During the course of the study, trace (0.5+) levels of anterior chamber cells were seen in 4 of 6 animals in the mid-dose group (250 µg/eye/dose) and 3 of 6 animals in the high-dose group (500 µg/eye/dose) in the multiple (biweekly) intravitreous dose prevention experiment and in 1 of 6 animals in the single intravitreous dose treatment study (500 µg/eye following CNV formation). Vitreous cell scores were also mild (0.5+ to 1+) in all of the groups that underwent intravitreous injection of VEGF Trap, but vitreous cells were more frequent and detected in all animals in these groups at some time during the study. This finding was not unexpected, because inflammatory cells are much slower to enter and clear from the more viscous vitreous gel than the aqueous humor. These results are summarized in Table 2. At no time or dose did the mean cell inflammatory score exceed 1+ in any eye. Ocular examinations were performed approximately 2 weeks following injections in the intravitreous prevention study, so early transient inflammation may have been missed. However, the animals in the intravitreous treatment group were examined 8 days after injection and only mild inflammation was observed (on study day 23) (Table 2). No animals showed gross evidence of ocular or systemic toxic effects based on daily cage-side inspections. There were no significant effects on intraocular pressure beyond a transient elevation in all groups immediately following intravitreous injection.

Intravenous administration of VEGF Trap placebo or VEGF Trap at a low or high dose produced no detectable anterior chamber or vitreous cells.

No evidence of a retinal inflammatory response (eg, perivascular sheathing, retinal thickening, optic nerve swelling, or retinal vascular leakage) was found on color fundus photography or FA in any of the animals.

## FLUORESCEIN ANGIOGRAMS

Of the 4 grades assigned to the laser treatment spots, grade 4 (bright hyperfluorescence early or midtransit, with late leakage extending beyond the borders of the laser spot) corresponds to clinically significant leakage. Grade 4 lesions are thought to reflect the presence of new choroidal vessels that either have grown beyond the laser treatment spot or are leaking so intensely that the fluorescein dye has spread markedly away from the vessels. The results with respect to grade 4 leakage for all groups are shown in **Table 3**. The average number of grade 4 lesions in the intravitreous placebo group ranged from 26.9% to 32.4% during the times evaluated (postlaser days 15, 20, and 29), while 45.4% to 50.0% of the laser treatment areas show grade 4 leakage in the intravenous placebo group. The mean percentage of grade 4 lesions in the control groups was similar to that which has been reported by others using this animal model of CNV.[10,11,13] By contrast, all of the VEGF Trap prevention groups showed marked reduction or complete absence of grade 4 lesions, irrespective of dose (**Figure 4** and **Figure 5**). **Table 4** shows the distribution of all lesion grades on day 29 for the prevention groups.

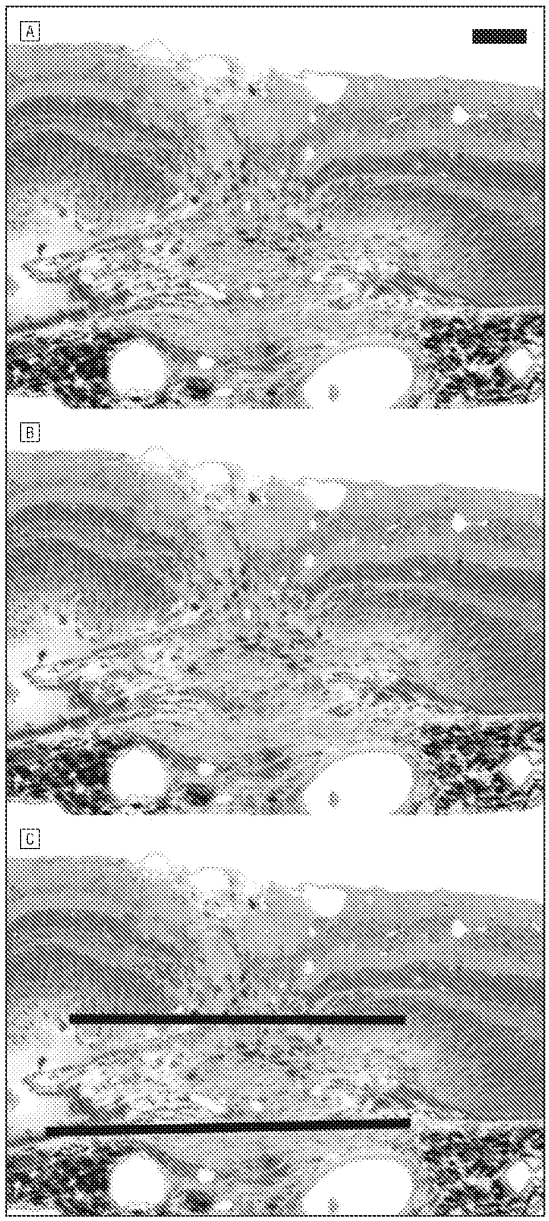


**Figure 3.** Semiquantitative scoring of lesions (glycol methacrylate sections stained with toluidine blue; scale bar=250 µm). A, Choroidal fibroplasia (pink). A score of 0 indicates none; 1, small, focal; 2, once the retinal thickness across; and 3, twice the retinal thickness across. B, Choroidal neovascularization (red). A score of 0 indicates none; 1, single small focus; 2, one tuft of vessels; and 3, multiple vessels extending once or twice the retinal thickness. C, Retinal elevation (distance between the lines). A score of 0 indicates none; 1, less than 0.2 times the retinal thickness; 2, less than 0.4 times the retinal thickness; and 3, less than 0.6 times the retinal thickness.

In the VEGF Trap treatment group (single intravitreous injection of VEGF Trap administered on postlaser day 15), 44.4% of laser treatment spots exhibited grade 4 leakage on day 15, similar to the percentage of grade 4 spots in the 2 placebo control groups. However, by postlaser day 20 (5 days following intravitreous administration of VEGF Trap), only 1.9% of the spots were grade

**Table 2. Inflammatory Response[a]**

| Group | Score, Mean (SD)[b] | | | | | |
|---|---|---|---|---|---|---|
| | Anterior Chamber Cells | | | Vitreous Cells | | |
| Intravenous prevention | Day 9 | Day 23 | Day 33 | Day 9 | Day 23 | Day 33 |
| Placebo | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 mg/kg/dose | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 mg/kg/dose | 0 | 0 | 0 | 0 | 0 | 0 |
| Intravitreous prevention | Day 7 | Day 21 | Day 32 | Day 7 | Day 21 | Day 32 |
| Placebo | 0 | 0 | 0 | 0.08 (0.2) | 0.04 (0.1) | 0.04 (0.1) |
| 50 µg/eye/dose | 0 | 0 | 0 | 0.71 (0.4) | 0.42 (0.3) | 0.46 (0.3) |
| 250 µg/eye/dose | 0.13 (0.2) | 0.04 (0.1) | 0.08 (0.1) | 0.63 (0.2) | 0.33 (0.4) | 0.50 (0.3) |
| 500 µg/eye/dose | 0 | 0.17 (0.2) | 0.17 (0.3) | 0.88 (0.1) | 0.67 (0.3) | 0.63 (0.4) |
| Intravitreous treatment | | Day 23 | Day 33 | | Day 23 | Day 33 |
| Single dose of 500 µg/eye | | 0.08 (0.2) | 0 | | 0.71 (0.4) | 0.50 (0.2) |

[a] The days indicate the days following laser treatment.

[b] Numerical scoring from 0 to 4 based on the number of cells observed per single field of focused slitlamp beam: a score of 0.5 indicates 1 to 5 cells; a score of 1, 5 to 25 cells; a score of 2, 25 to 50 cells; a score of 3, 50 to 100 cells; and a score of 4, more than 100 cells. Scores from both eyes were averaged per animal, and the means and standard deviations are based on 6 animals per group. Anterior chamber or vitreous cells were not observed before dosing in any group.

**Table 3. Mean Percentages of Grade 4 Lesions by Group**

| Group | Grade 4 Lesions, Mean %[a] | | |
|---|---|---|---|
| | Day 15 | Day 20 | Day 29 |
| Intravenous prevention[b] | | | |
| Placebo | 45.4 | 50.0 | 45.4 |
| 3 mg/kg/dose | 0[c] | 0[c] | 0.9[d] |
| 10 mg/kg/dose | 0[c] | 0[c] | 0[c] |
| Intravitreous prevention[e] | | | |
| Placebo | 32.4 | 31.5 | 26.9 |
| 50 µg/eye/dose | 0[c] | 0.9[d] | 0.9[d] |
| 250 µg/eye/dose | 0[c] | 0[c] | 0[c] |
| 500 µg/eye/dose | 0[c] | 0[c] | 5.6[d] |
| Intravitreous treatment | | | |
| Single dose of 500 µg/eye | 44.4 | 1.9[f] | 0[g] |

[a] Mean percentages of grade 4 lesions by treatment group are shown across fluorescein angiography intervals (postlaser days).

[b] *P* values for trend test for the intravenous prevention days 15, 20, and 29 were <.001, <.001, and .002, respectively (decreasing trend).

[c] Significant difference (1-sided $P < .008$) of the treatment group (intravenous prevention or intravitreous prevention) from the relevant control group using Fisher exact test.

[d] Significant difference (1-sided $P < .04$) of the treatment group (intravenous prevention or intravitreous prevention) from the relevant control group using Fisher exact test.

[e] *P* values for trend test for the intravitreous prevention days 15, 20, and 29 were < .001, < .001, and .008, respectively (decreasing trend).

[f] Wilcoxon signed rank test for comparison between the intravitreous prevention placebo group and intravitreous treatment group showed a significant decrease in grade 4 lesions on day 20 (1-sided $P < .01$).

[g] Wilcoxon signed rank test for comparison between the intravitreous prevention placebo group and intravitreous treatment group showed a significant decrease in grade 4 lesions on day 29 (1-sided $P < .003$).

4; no spots were grade 4 at day 29 (Table 3, **Figure 6**, and **Figure 7**). When all lesion grades were compared, there was a marked shift from mostly grades 4 and 3 in the day 15 (pretreatment) angiograms to mostly grades 2 and 1 in the day 29 angiograms (**Figure 8**).

### RETINAL HISTOLOGICAL EVALUATION

Consonant with the FA findings, histological evaluation revealed that intravitreous administration of VEGF Trap reduced proliferative responses of the retina to laser injury, particularly neovascular proliferation.

When VEGF Trap administration was begun prior to laser injury (prevention), choroidal fibroplasia and retinal elevation scores as well as CNV scores were all significantly lower in VEGF Trap–treated animals relative to placebo controls (**Table 5** and **Figure 9**). When a single injection of VEGF Trap was given after grade 4 lesions had developed, there was also a trend toward decreased CNV, but mean scores for fibroplasia and retinal elevation were not significantly different from controls (Table 5 and **Figure 10**).

## COMMENT

### BACKGROUND

Important advances were made in the treatment of AMD by the application of drugs that act to destroy and/or prevent formation of the new blood vessels. The first of these to be approved for human use was photodynamic therapy using the photosensitizing dye verteporfin (Visudyne; Novartis, Basel, Switzerland) administered intravenously followed by exposure of the CNV to 689-nm low-energy laser. Photodynamic therapy greatly reduced direct retinal damage from prior thermal laser therapy. However, there were problems with recurrence, and patients continued to have a decline in vision over time.[14]

Following the development of photodynamic therapy, a new family of drugs that act to inhibit the cytokine VEGF-A was developed. VEGF-A has been implicated as a causal factor in the development of the wet form of AMD as well as other ocular vascular diseases characterized by pathological neovascularization and vascular leak and/or edema. A number of strategies are being developed to inhibit VEGF-A signaling in these conditions, including application of antibodies to VEGF-A or the VEGF receptors, VEGF-binding aptamers, and small interfering RNAs and treatment with kinase inhibitors. The first of these

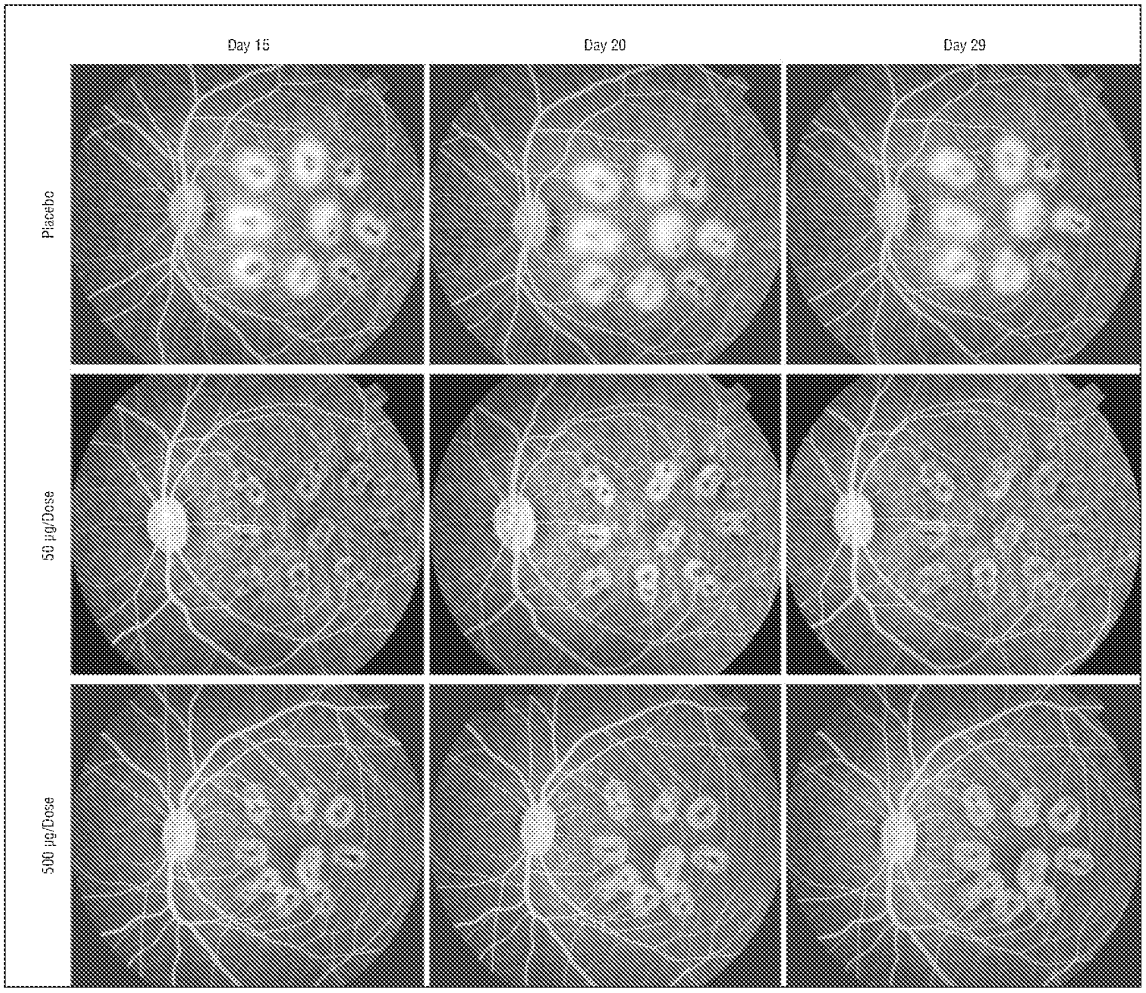


**Figure 4.** Intravitreous prevention (repeated injection) study, showing late-phase fluorescein angiograms at postlaser days 15, 20, and 29 for 3 representative animals in the indicated groups. The placebo-treated animal shows grade 4 leakage in most of the 9 treatment areas, whereas the animals in the groups receiving doses of 50 µg/eye and 500 µg/eye show no grade 4 leakage in any laser treatment areas at any of the 3 times.

to be approved for human use was pegaptanib (Macugen), an RNA aptamer directed against the VEGF-A 165 isoform.[15,16] Inhibition of VEGF-A 165 was shown to slow the progression of vision loss in wet AMD but did little to reverse vision loss. More recently, intravitreous administration of ranibizumab (Lucentis) has been approved for the treatment of AMD. Ranibizumab is a humanized monoclonal antibody Fab fragment that is directed against all isoforms of VEGF-A. It has largely replaced pegaptanib in clinical practice following 2 large, clinical, phase 3 trials (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD [MARINA][17] and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD [ANCHOR][18,19]) showing that 94% to 96% of patients receiving 0.5 mg of ranibizumab monthly lost fewer than 15 letters of visual acuity and 34% to 40% actually gained 15 letters. The related drug bevacizumab (Avastin), a humanized whole IgG1 antibody approved for oncology, is also used off label by clinicians.[20] Despite these advances, the current treatment of choice for AMD (either ranibizumab or bevacizumab) requires repeated intravitreous injections on a monthly basis for an indeterminate period—possibly years—to maintain improvements in visual acuity.

## VEGF, PlGF, AND CNV

Extensive literature demonstrates that VEGF-A is a critical factor contributing to the development of ocular neovascularization (for a review, see the article by Witmer et al[21]). In contrast to other agents that bind and neutralize only VEGF-A, VEGF Trap also binds and neutralizes PlGF.[9] Placental growth factor is a member of the VEGF family of cytokines that is expressed prominently in the placenta, the tissue from which it was first isolated.[22] It can promote angiogenesis directly or by enhancing VEGF-A activity.[23-25] In contrast to VEGF-A, which also plays an indispensible role in normal vascular development, PlGF has been specifically implicated

in promoting pathological neovascularization. While genetic deletion of even a single allele of VEGF-A results in profound impairments in vascular development, normal vascular development and function are not appreciably impaired in PlGF-null mice. However, genetic deletion or pharmacological inhibition of PlGF significantly reduces pathological neovascularization as well as the associated vascular leakage in numerous disease settings.[26] Like VEGF-A, PlGF appears to be involved in promoting ocular vascular disease in both humans and animals. For example, PlGF is present in CNV membranes excised from human eyes,[27] and experimental CNV is decreased in PlGF-null mice and mice treated with PlGF neutralizing antibodies relative to controls.[28]

The proangiogenic and propermeability effects of VEGF-A are thought to be mediated primarily through VEGFR2 expressed on vascular endothelial cells. A structurally related receptor, VEGFR1, binds both VEGF-A and PlGF. In addition to being present on endothelial cells, where receptor ligation is also thought to promote angiogenesis and vascular permeability, albeit more weakly, VEGFR1 is expressed by many other cell types including leukocytes, pericytes, smooth muscle cells, and endothelial progenitor cells.[29] Thus, in addition to promoting angiogenesis and vascular permeability by acting directly on endothelial cells, VEGF and PlGF can also act via VEGFR1 on a variety of other cell types involved in blood vessel formation and stabilization. Moreover, VEGF and PlGF serve as potent chemoattractants and activators of leukocytes, particularly monocytes, in a variety of pathological conditions.[29,30]

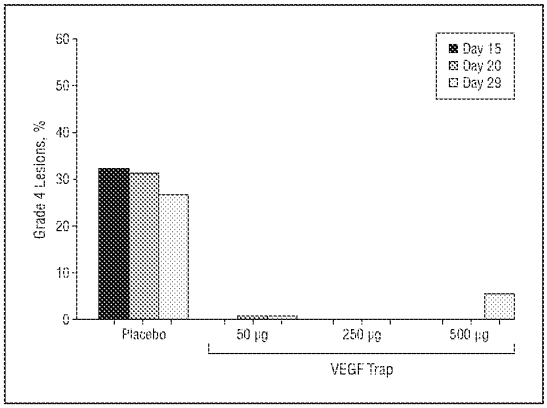


**Figure 5.** Percentage of grade 4 lesions at postlaser days 15, 20, and 29 for groups that received intravitreous placebo and VEGF Trap prevention.

## EFFECTS OF VEGF TRAP IN RODENT MODELS OF OCULAR NEOVASCULARIZATION

VEGF Trap, administered either as serial subcutaneous injections or as a single intravitreous injection, has been shown to suppress laser-induced CNV in mice.[31] Moreover, VEGF Trap given subcutaneously inhibits retinal neovascularization in transgenic mice that overexpress VEGF in photoreceptors. Furthermore, VEGF Trap was found to reduce breakdown of the blood-retinal barrier following intravitreous injection of VEGF and in transgenic mice that overproduce VEGF in the retina.[31] Systemic administration of VEGF Trap also has been shown to suppress neovascularization and the associated inflammatory cell infiltrate following corneal injury[32] and to delay corneal allograft rejection in mice.[33] More recently, VEGF Trap has been reported to prevent the development and promote the regression of recently formed CNV following subretinal injection of matrigel in rats.[34] Interestingly, VEGF Trap treatment also reduced CNV-associated fibrosis and inflammation in this model.

## THIS STUDY

Although CNV can be induced in other species,[35-37] only nonhuman primates have maculae similar to the human macula. Thus, the model by Ryan[11] of inducing CNV using intense, small laser spots applied to the macular retina to break the Bruch membrane has become a standard means of assessing the preclinical efficacy of pharmacological treatments for wet AMD (ie, CNV). For example, this model was used for preclinical evaluations of photodynamic therapy[38-41] and Lucentis.[10] Even so, the model has its limitations. The young nonhuman primates have otherwise healthy retinae (including retinal pigment epithelia) and the induced CNV, unlike CNV in elderly humans with AMD, is self-limiting, resolving in 6 to 8 weeks without treatment. Also, the model has considerable variability. Only about 40% of the treatment spots go on to develop grade 4 lesions[11] and 20% of the animals are nonresponders, with no CNV developing in either eye (T.M.N. and B.J.C., unpublished data, May 2008). Therefore, it is important to have an adequate number of subjects in each group.

**Table 4. Percentages of All Grades of Choroidal Neovascular Lesions in the Prevention Groups at Postlaser Day 29**

| Group | Lesion Grade, % | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Intravenous prevention | | | | |
| Placebo | 27.8 | 23.1 | 3.7 | 45.4 |
| 3 mg/kg/dose | 87.0 | 11.1 | 0.9 | 0.9 |
| 10 mg/kg/dose | 73.2 | 25.9 | 0.9 | 0.0 |
| Intravitreous prevention | | | | |
| Placebo | 56.5 | 10.2 | 6.5 | 26.9 |
| 50 µg/eye/dose | 83.3 | 15.7 | 0.0 | 0.9 |
| 250 µg/eye/dose | 75.9 | 22.2 | 1.9 | 0.0 |
| 500 µg/eye/dose | 79.6 | 13.0 | 1.9 | 5.6 |