

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FRESENIUS KABI SWISSBIOSIM GMBH,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case: IPR2025-01269
U.S. Patent No. 10,828,345

EXPERT DECLARATION OF DR. NEIL M. BRESSLER
IN SUPPORT OF PATENT OWNER PRELIMINARY RESPONSE

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TABLE OF EXHIBITS

Exhibit	Description
2001	Certified File History of U.S. Patent No. 10,828,345 B2
2002	Comparison between April 28, 2009 and December 1, 2009 Clinicaltrials.gov Record Histories for NCT00509795, <i>available at https://clinicaltrials.gov/study/NCT00509795?term=NCT00509795&rank=1&tab=history&a=9&b=10#version-content-panel</i> .
2003	“Information from ClinicalTrials.gov archive on the view of NCT00509795 ‘Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD)’ (12-01-2009)” excerpted from file history of U.S. Patent Application No. 14/972,560.
2004	Donald Trump Remarks Transcript, Calls Contracting COVID-19 “Blessing from God” October 7, https://www.rev.com/transcripts/donald-trump-remarks-transcript-calls-contracting-covid-19-blessing-from-god-october-7 (last visited September 18, 2025).
2005	Kiran Stacey, David Crow, and Donato Paolo Mancini, <i>Regeneron: the company that Trump claims cured his Covid</i> , Financial Times, October 9, 2020, https://www.ft.com/content/70672ed3-bf66-4c14-8392-076d0c503558 .
2006	Kiran Stacey, <i>Trump calls Coronavirus treatment he received a “cure”</i> , Financial Times, October 7, 2020, https://www.ft.com/content/a792326c-40e7-460d-ac38-8a9b03286ea0 .
2007	U.S. Provisional Application No. 61/432,245

Exhibit	Description
2008	U.S. Provisional Application No. 61/434,836
2009	U.S. Provisional Application No. 61/561,957
2010	Eylea Label (November 18, 2011)
2011	P.J. Rosenfeld et al., <i>Ranibizumab for Neovascular Age Related Macular Degeneration</i> , 355 N. ENG. J. MED. 1419 (2006)
2012	C.D. Regillo et al., <i>Randomized, Double-Masked, Sham-Controlled Clinical Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 1</i> , 145 AM. J. OPHTHALMOLOGY 239-248 (2008)
2013	N. M. Bressler, <i>Antiangiogenic Approaches to Age-Related Macular Degeneration Today</i> , 116 AM. ACAD. OPHTHALMOLOGY S15 (2009)
2014	Curriculum Vitae of Dr. Neil M. Bressler, M.D.
2015	Expert Declaration of Dr. Neil M. Bressler in Support of Patent Owner Preliminary Response.
2016	MACUGEN® Prescribing Information (2006)
2017	SUSTAIN - Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (Dec. 09, 2010), https://www.clinicaltrials.gov/study/NCT00331864?tab=history&a=10#version-content-panel

Exhibit	Description
2018	A.P. Adamis, <i>Angiogenesis and Ophthalmic Disease</i> , 3 ANGIOGENESIS 9 (1999)
2019	G.L. Skuta et al, <i>Retina And Vitreous</i> 72-73, 109-114, 121, 128-29 (Section 12, 2009)
2020	Barbazetto et al., <i>Dosing Regimen and the Frequency of Macular Hemorrhages in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab</i> , 30 RETINA 1376 (2010).
2021	P.J. Patel et al., <i>A Randomised, Double-Masked Phase III/IV Study of the Efficacy and Safety of Avastin® (Bevacizumab) Intravitreal Injections Compared to Standard Therapy in Subjects with Choroidal Neovascularization Secondary to Age-related Macular Degeneration: Clinical Trial Design</i> , 9 BIOMED CENT. 56 (2008)
2022	Prospective OCT Study with Lucentis for Neovascular AMD (PrONTO study), NCT00344227, ClinicalTrials.gov (June 23, 2006), https://clinicaltrials.gov/study/NCT00344227?tab=history&a=1#version-content-panel

I. Introduction and Assignment

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 in connection with the Petition for Inter Partes review (“IPR”) filed by Fresenius Kabi Swissbiosim GmbH (“Fresenius”) challenging all claims of Regeneron’s U.S. Patent No. 10,828,345 (the “’345 patent”) (EX1001).

2. 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 the IPR is instituted. In particular, if trial is instituted, I understand that Regeneron will have the opportunity to submit a Patent Owner Response and may choose to support that Response with a declaration from me or another technical expert that is not limited to the issues or opinions set forth below.

3. In this preliminary setting, I was asked to provide my opinion as to certain limited questions. In particular, I was asked to do the following:

- Provide a brief overview of the state of the art for the treatment of angiogenic eye disorders as of the relevant priority date;
- Provide my opinion as to whether a person of ordinary skill in the art (“POSA”) as of the priority date of the ’345 patent would have understood

four references—Dixon (EX1007); NCT-377 (EX1018); NCT-795 (EX1017), and Regeneron (8-May-2008) (EX1022)—to disclose every limitation of challenged claims 1-9, as set forth in Grounds 1-4 of Fresenius's Petition;

- Provide my opinion as to whether the POSA as of the priority date of the '345 patent would have found the inventions of challenged claims 1-9 to have been obvious in view of Dixon in combination with NCT-377, for the reasons set forth in Ground 5 of Fresenius's Petition; and
- Provide my opinion as to whether the POSA as of the priority date of the '345 patent would have found the inventions of challenged claims 10 and 11 to have been obvious in view of any one of Dixon, NCT-377, NCT-795, and Regeneron (8-May-2008) in combination with Regeneron (18-Feb-2010), for the reasons set forth in Grounds 6-9 of Fresenius's Petition.

4. In forming my opinions, I reviewed Fresenius's Petition, the declaration of Dr. John Galanis (EX1003) submitted in support thereof, all the materials cited in the Petition and Dr. Galanis's declaration, and all the materials cited herein. My opinions and views set forth below also are based on my decades of education, training, research, and clinical experience in ophthalmology, specifically in researching and treating retinal diseases.

5. Below I respond to certain of Dr. Galanis's opinions as set forth in his declaration, as well as certain statements made by Fresenius in the Petition. I have not, however, undertaken to respond to *every* statement in Dr. Galanis's declaration or every technical assertion in Fresenius's Petition. My silence as to any such opinion or assertion should not be understood to mean that I agree with it.

6. Likewise, at this preliminary stage, I do not undertake below to set forth every basis for my opinions or every reference, fact, etc., that supports them. In the event that trial is instituted, I expect to provide opinions in addition to those set forth below, as well as additional support, explanation, and detail related to the opinions contained herein.

7. I am being paid at an hourly rate of \$1100 for my work on this matter. I have no personal or financial stake in the outcome of the present proceeding. My compensation does not depend in any way on the outcome of this proceeding.

II. Qualifications and Experience

8. I am a Professor of Ophthalmology in the Department of Ophthalmology, Wilmer Eye Institute at Johns Hopkins University School of Medicine. I have been on the full time, tenure track faculty at Johns Hopkins University since 1988. From 2005 to 2018, I served as Chief of the Retina Division of the Department of Ophthalmology at Johns Hopkins School of Medicine. As a physician-scientist, I have received numerous honors and awards from national and

international ophthalmology societies in recognition of my expertise in retinal diseases, particularly in clinical trials related to diabetic retinopathy and macular degeneration. In addition to conducting my own research as Chair of numerous collaborative, multicenter, national, and international trials sponsored by the National Institutes of Health, I also am the Editor in Chief of JAMA Ophthalmology, one of the leading peer-reviewed scientific journals in the field of ophthalmology.

9. Throughout my career, I have chaired numerous clinical trials and published hundreds of peer-reviewed scientific articles not only in ophthalmology journals but also in general medical journals such as the New England Journal of Medicine and JAMA (the Journal of the American Medical Association).

10. I also have testified before the U.S. House of Representatives Committee on retinal diseases as a medical expert.

11. I graduated from the University of Michigan with a Bachelor of Science degree in 1978 and earned my medical degree from Johns Hopkins School of Medicine in 1982.

12. After graduating from medical school and completing a one-year internship in the Department of Medicine at Johns Hopkins Hospital, I completed an ophthalmology residency at Harvard Medical School's Massachusetts Eye and Ear Infirmary in 1986 and a medical retina fellowship at the Wilmer Eye Institute in

1987. From 1987 to 1988, I worked as a faculty member for Harvard Medical School, while continuing and completing my training in surgical retina.

13. I then joined the Retina Division of Johns Hopkins University School of Medicine (Department of Ophthalmology, Wilmer Eye Institute) as Assistant Professor in 1988. I was promoted to Associate Professor in 1991 and to Professor in 1997.

14. In 2000, I received the inaugural James P. Gills Professorship of Ophthalmology. From 2005 to 2018, I served as Chief of the Retina Division, which included 18 full-time retina physicians as well as over 50 clinical and 40 research staff.

15. In addition to my work at Johns Hopkins School of Medicine, I was the President of the Macula Society in 2013 and 2014, after serving as its Program Chair for nine years.

16. As a practicing ophthalmologist and retinal specialist with over 38 years of clinical practice, I am regarded by my peers as a leading expert in diabetic retinopathy and macular degeneration. I have evaluated and treated thousands of patients with diabetic retinopathy and the neovascular (“wet”) age-related macular degeneration (wAMD). I have administered thousands of anti-VEGF intravitreal injections to treat those conditions.

17. My expertise includes building best treatment management plans for individuals with diabetic retinopathy, the leading cause of irreversible blindness, if left untreated, in working-age adults, and wAMD, the leading cause of irreversible blindness, if left untreated, among older individuals in developed countries. Currently, I continue to maintain an active national and international referral practice for retinal diseases.

18. My primary research interests for over 35 years have been designing, operating, and reporting results of clinical trials for common retinal diseases, including age-related macular degeneration and diabetic retinopathy. I have served as Chair and Principal Investigator of the Chair's Office for many multicenter randomized clinical trials, including three clinical trials in wAMD and related diseases sponsored by the National Eye Institute of the National Institute of Health (NIH), one clinical trial in dry AMD sponsored by the industry, and seven randomized clinical trials that were sponsored by the National Eye Institute.

19. To date, I have authored almost 500 peer-reviewed publications on a wide range of topics related to diagnosing and treating retinal diseases, including imaging of retinal diseases, treatment regimens of common retinal disease, reviews in JAMA and the New England Journal of Medicine, and more recently, cutting-edge AI research in the field of retina. Specifically, in the areas of age-related macular degeneration and diabetic retinopathy, I have authored over 150 peer-

reviewed clinical research publications in wAMD and over 150 in diabetic retinopathy, most of which were from randomized clinical trials, the apex of study designs for evidence-based medicine. For example, in diabetic retinopathy, clinical trials from the NIH-sponsored Diabetic Retinopathy Clinical Research Network not only defined the treatment regimen and management of diabetic macular edema and proliferative diabetic retinopathy but also were the basis of guidelines in the management of diabetic macular edema and proliferative diabetic retinopathy.

20. As a leader in clinical research, I have overseen research and publications in the field of ophthalmology and beyond. Since 2013, I have been the Editor in Chief of JAMA Ophthalmology and a member of the JAMA Network Editorial Board. JAMA Ophthalmology is one of the foremost peer-reviewed medical journals that covers all aspects of ophthalmology. It is published by the American Medical Association, whose affiliation dates back to 1929, and I am its ninth Editor in Chief. Over the past several years while I have been the Editor in Chief, the articles published by JAMA Ophthalmology has had millions of views and downloads, and related podcasts separately had thousands of downloads. JAMA Ophthalmology also is mentioned in mainstream news and social media more than any other ophthalmology journal in the world.

21. Since 2003, I also have served on the National Eye Institute's Data and Safety Monitoring Committee for intramural clinical trials, where I was Chair for

over 20 years. The Committee ensures the safety of study participants during clinical trials by providing oversight and feedback to investigators in the design, operation, and reporting of clinical trial outcomes.

22. From 2006 to 2012, I served as Chair of the NIH-sponsored Diabetic Retinopathy Clinical Research Network, the largest ophthalmology network of multicenter randomized clinical trials. In that role, I was responsible for establishing guidelines, policies, and protocols for conducting retina-related clinical research and for implementing them, fostering academic integrity and optimal clinical trial performance. During my time, the Network successfully completed 20 studies, including randomized clinical trials sponsored by the National Eye Institute. These studies have been instrumental in shaping clinical practice guidelines in diabetic retinopathy and diabetic macular edema around the world. The Network, as a whole, oversaw over 100 ophthalmology clinical sites and over one thousand investigators and study personnel across the United States.

23. I served on the FDA Ophthalmic Devices Panel for 24 years, including two terms as Chair from 2008 to 2011 and again from 2019 to 2022. The Ophthalmic Devices Panel reviews and evaluates the safety and effectiveness of investigational and marketed devices intended for use in the eyes. The panel then makes appropriate recommendations to the FDA Commissioner on whether the benefits of these

devices outweigh the risks to patients—a crucial consideration in FDA approval decisions.

24. In addition to research and clinical practice, I have supervised 97 ophthalmologists specializing in retina, as well as over 185 ophthalmology residents and mentored retina specialists in clinical research, many of whom became leaders in retina practices, retina societies, and department chairs both within the United States and internationally. I also serve as the Program Director for three annual Continuing Medical Education meetings for Johns Hopkins University, which recently have had more than 1,000 on-line registrants each year. In this role, I develop programs directed to teaching the latest treatment regimens and clinical studies in wAMD and diabetic retinopathy. I also have lectured at numerous institutions and society meetings around the world on treating wAMD and diabetic retinopathy.

25. A current copy of my curriculum vitae is included at EX2014 and sets forth my qualifications and experience in further detail.

III. Legal Standards

26. I am not an expert in the law. The legal standards I have applied were explained to me by counsel for Patent Owner.

A. Anticipation

27. I have been informed that a patent claim is “anticipated,” and thus invalid, if a single prior art reference discloses every limitation of the claimed invention as arranged in the claim.

28. I have been informed that prior art may inherently anticipate a claimed invention without expressly disclosing a feature of the claimed limitation if that missing characteristic necessarily is present in the prior art reference. I also have been informed that inherency cannot be invoked by mere possibilities or probabilities, but rather, the missing limitation must be there each and every time without exception.

B. Obviousness

29. I have been informed that a patent claim may be invalid for obviousness if the differences in the subject matter between the claimed invention and the prior art references are such that the subject matter as whole would have been obvious to a person of ordinary skill at the time the invention was made. I also am informed that in determining obviousness, I should consider the following factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the pertinent art; (4) any objective indicia of non-obviousness, including unexpected results, commercial success, long-

felt but unresolved needs, failure of others, skepticism of others about the invention, and later praise of that invention.

30. I have been informed that obviousness must be assessed based on the knowledge possessed by the POSA at the time when the invention was made. In other words, it is impermissible to use hindsight-based knowledge of the claimed invention to determine questions of obviousness. Relatedly I understand that the inventor's path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the POSA would have followed, as evidenced by the pertinent prior art.

31. I have been informed that, when a party challenging a patent relies on multiple references to demonstrate that an invention would have been obvious to the POSA, the challenger must prove not only that the prior art as a whole taught or suggested the invention, but also that the POSA would have had reason to select the prior art references on which the challenger relies and to combine the teachings of the prior art references to achieve the claimed invention. In other words, there needs to be a reason to combine the known elements in the way claimed by the invention.

32. I understand from counsel that, in addition to having a motivation to achieve the claimed invention, the POSA who is following the reference or references that purportedly make it obvious must have had a reasonable expectation of success in practicing the invention to solve the POSA's goals. I understand from

counsel that to have a reasonable expectation of success, one must be motivated to do more than merely vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

33. I have been informed that references that “teach away” from the claimed invention—in other words, references that would lead the POSA in a different direction from that taken by the inventor—must be considered. I also understand that a prior art reference teaches away from the claimed invention if the POSA, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that would lead to the claimed invention. I understand that in general, a reference will teach away if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of a result sought by the claimed invention. In determining whether the claimed invention would have been obvious, one must consider the prior art as a whole, and must consider any individual reference for its whole disclosure.

34. I have been informed that a claim limitation may be obvious if the limitation necessarily must be present, or the natural result of a combination of elements explicitly disclosed in the prior art. However, I also understand that that

which may be inherent is not necessarily known and that which is unknown cannot be obvious.

IV. The '345 Patent

A. Challenged Claims

The '345 patent includes eleven claims, reproduced 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 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered 12 weeks after the immediately preceding dose;
wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.
2. The method of claim 1, wherein the VEGF antagonist is aflibercept.
3. The method of claim 1, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.
4. The method of claim 3, wherein the intraocular administration is intravitreal administration.
5. The method of claim 4, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.
6. The method of claim 5, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

7. The method of claim 5, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.
8. The method of claim 5, 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.
9. The method of claim 8 wherein the angiogenic eye disorder is age related macular degeneration.
10. The method of claim 8 wherein the angiogenic eye disorder is diabetic retinopathy.
11. The method of claim 8, wherein the angiogenic eye disorder is diabetic macular edema.

EX1001 at 21:55-23:12.

B. Priority Date and Prior Art

35. I am informed that the '345 patent claims priority on its face to the following provisional applications:

- provisional Application 61/432,245, filed on January 13, 2011 (EX2007);
- provisional application 61/434,836, filed on January 21, 2011 (EX2008);
- provisional application 61/561,957, filed on November 21, 2011 (EX2009).

36. I understand Petitioner asserts that the '345 patent claims priority to January 21, 2011. Pet. at 12 n.1. In my opinion, the subject matter recited in the

challenged claims of the '345 patent was described in provisional application No. 61/432,245 filed on January 13, 2011. At a minimum, I note that the January 13, 2011 provisional application discloses that “[i]n one exemplary embodiment of the present invention, **each secondary dose is administered** 2 to 4 (**e.g., 2, 2 1/2, 3, 3 1/2, or 4**) **weeks after the immediately preceding dose, and each tertiary dose is administered** at least 8 (**e.g., 8, 8 1/2, 9, 9 1/2, 10, 10 1/2, 11, 11 1/2, 12, 12 1/2, 13, 13 1/2, 14, 14 1/2, or more**) **weeks after the immediately preceding dose.**” EX2007 at ¶ 16 (emphases added). As the POSA would have understood, these statements describe a regimen in which secondary doses are administered four weeks after the immediately preceding dose, and tertiary doses are administered twelve weeks after the immediately preceding dose, just as the challenged claims require.

37. I have reviewed the Petition and Dr. Galanis’s declaration, and do not see any explanation as to why the January 13, 2011 provisional does not adequately describe the invention of the challenged claims.

38. In his report, Dr. Galanis states that he has “been asked to assume, for purposes of my analysis and coming to my opinions, that the priority date of the 345 patent is November 21, 2011.” EX1003 at ¶ 64. Dr. Galanis does not explain why he was asked to assume a priority date of November 21, 2011 and, as I said above, I do not see any explanation in his report as to why the January 13, 2011 provisional application does not adequately describe the invention of the challenged claims. Dr.

Galanis also does not explain whether and how his opinions would have differed had he applied a January 13, 2011 or January 21, 2011 priority date rather than a November 21, 2011 priority date.

39. I am informed that if a printed publication was publicly accessible more than one year before the earliest-filed application to which the challenged patent properly claims priority, it is prior art. If a reference was *not* publicly accessible more than one year before the earliest-filed application to which the challenged patent properly claims priority, I understand the reference may not be prior art.

40. I understand that Regeneron asserts in its Preliminary Response that Fresenius has not met its burden to establish whether Regeneron (18-Feb-2010) is prior art. I have not been asked to analyze whether Regeneron (18-Feb-2010) is prior art, nor have I been asked to determine whether Fresenius and/or Dr. Galanis has established that Regeneron (18-Feb-2010), submitted as EX1052, became publicly available to those of skill in the art as of February 18, 2010. Instead, for purposes of forming my opinions in this declaration, I have been asked to assume that Regeneron (18-Feb-2010) is prior art, notwithstanding Regeneron's argument that Fresenius failed to establish as such.¹

¹ I have been asked to make the same assumption as to Massin (EX1044), another cited reference that was not published more than one year before January 13, 2011 or January 21, 2011. That is, I have been asked to assume that Massin is prior art.

41. For the sake of simplicity, I will refer to a “January 2011” priority date throughout my declaration, because January 21, 2011 appears to be the date on which Fresenius intended to rely, based on its express statement in the Petition at page 12, note 1, and because I believe the ’345 patent is entitled to claim priority to the January 13, 2011 provisional application. However, my opinions as set forth below would not change if I were to evaluate the prior art from any date between January 13, 2010 and November 21, 2011.²

42. As set forth below, it is my opinion that challenged claims 10 and 11 would not have been obvious in view of any one of Dixon, NCT-377, NCT-795 or Regeneron (8-May-2008) in combination with Regeneron (18-Feb-2010) and “a POSA’s knowledge,” even assuming that Regeneron (18-Feb-2010) is prior art. If

My opinions as set forth below would not change if it were to be determined that Massin is not prior art.

² I am informed that the date as of which references are considered prior art may be up to one year before the earliest-filed application depending on when the invention was made and/or whose work the potential prior art reference reflects. Thus, I understand Regeneron *may* argue that references published after January 13, 2010 are not prior art. I have not undertaken any analysis as to whether a given reference qualifies as prior art, and as I state above, my opinions as set forth in this declaration would not change if I evaluated the prior art as of any date between January 13, 2010 and November 21, 2011.

Regeneron (18-Feb-2010) were determined not to be prior art, it would remain my opinion that challenged claims 10 and 11 would not have been obvious to the POSA.

C. The Person of Ordinary Skill in the Art

43. I have been informed that the disclosures of the '345 patent should be viewed from the perspective of a person of ordinary skill in the art ("POSA") at the time of the claimed invention.

44. For the purpose of preparing this declaration in support of Patent Owner's Preliminary Response, I have been asked to apply Dr. Galanis's definition of a person of ordinary skill in the art. Under his definition, a POSA 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. EX1003 at 8. Additionally, Dr. Galanis's definition includes that 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: (1) developing treatments for angiogenic eye disorders, such as AMD and diabetic retinopathy, including through the use of VEGF antagonists, or (ii) treating of angiogenic eye disorders through the use of VEGF antagonists. *Id.*

45. I have met the above qualifications and thus have had at least the skills and experience of the POSA as defined by Dr. Galanis at all relevant times.

D. Claim Construction

46. For purposes of rendering my opinions, I have been asked to adopt the claim constructions provided in the Petition. Pet. at 21-22. In particular, I assume for purposes of this declaration that:

(1) the preamble, “[a] method for treating an angiogenic disorder in a patient” is limiting;

(2) the term “treating” means “administering a therapeutic to a patient, without a specific degree of efficacy required”; and

(3) the terms “initial dose,” “secondary dose,” and “tertiary dose” “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 dose’ are the doses which are administered after the initial dose; and the ‘tertiary doses’ are the doses which are administered after the secondary doses.” *Id.*

V. State of the Art

47. Below I provide a brief overview of the state of the art for the treatment of angiogenic eye disorders as of January 2011. I reserve the right to offer additional

opinions regarding the state of the art, or to expound on any opinions offered below, in a later declaration if institution is granted.

A. Angiogenic Eye Disorders

48. Angiogenic eye disorders are a group of diseases characterized by the growth of abnormal blood vessels in the eyes and vascular leakage from damaged, pre-existing blood vessels, both of which can and often do lead to severe vision loss. EX2018 at 1; EX1025 at 1.

49. Angiogenesis refers to the formation of new blood vessels from pre-existing vasculature and may be accompanied by growth of scar tissues. EX2018 at 1; EX2019 at 19, 24. Wet Age-Related Macular Degeneration (wAMD) is an angiogenic eye disorder characterized by the growth of abnormal and fragile blood vessels, often with ingrowth of scar tissues when left untreated, in the central part of the retina called the macula. EX2011 at 2; EX2019 at 19; EX2018 at 4. These fragile new vessels are prone to breaking and leaking fluid, damaging the macula or scarring the retina. EX2019 at 19; EX2018 at 4. Because the macula forms the center of the retina essential for sharp vision, such accumulation of fluid can lead to visual distortions or vision loss of the part of the retina (the macula) used, for example, to read, drive, see, or recognize faces. EX2018 at 4.

50. Diabetic retinopathy is a complication of diabetes that affects the blood vessels in the retina. EX2019 at 37-38. Diabetes can cause elevated sugar levels in

the blood, leading to hypoxia in the blood vessels that supply oxygen to retinal cells. EX1026 at 1. When oxygen-deprived, cells up-regulate expression of VEGF. EX1026 at 1. There are two stages of diabetic retinopathy, either of which may be accompanied by diabetic macula edema. *Id.* at 2; EX2018 at 11. The two stages are termed non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). EX1026 at 2.

51. Non-proliferative diabetic retinopathy includes closure of retinal capillaries that often may be recognized as dot and blot hemorrhages in the retina, or nerve fiber layer infarcts of the inner layer of the retina. EX2019 at 39. As capillary closure becomes more severe, retinal abnormalities reflect this severe loss of capillary perfusion within the central and peri-central portion of the retina, including the macula, exhibiting extensive hemorrhages, beading of the retinal veins, or intraretinal microvascular abnormalities (IRMA)—a proliferation of new capillaries within the substance of the retina tissue. *Id.* These latter three signs are considered severe non-proliferative diabetic retinopathy, and eyes with severe NPDR have a higher chance of developing proliferative diabetic retinopathy and diabetic macular edema than eyes with NPDR without signs considered severe NPDR. *Id.* at 14-16.

52. In the proliferative stage of diabetic retinopathy, the retina begins to form new blood vessels, a process called retinal neovascularization. EX1026, Figure

1; EX2019 at 43. These fragile blood vessels can cause bleeding into the vitreous, a jelly-like substance that fills the middle of the eye, causing patients to see dark floaters or lose central or peripheral vision or both. EX1026 at 1-2, 5. If the bleeding worsens, it may block significant parts of a patient's vision. *Id.* at 2. If not cleared spontaneously or with injection of anti-VEGF agents, patients may require a surgical removal of the blood (a procedure called vitrectomy). EX2019 at 47.

53. Some patients with diabetic retinopathy may develop a condition called diabetic macular edema. EX1026 at 1. Macular edema refers to the accumulation of fluid in the macula, which may be accompanied by lipid (lipoproteins within the fluid that may precipitate and become apparent as the edema resorbs). EX2019 at 39. While multiple conditions can cause macular edema, when the underlying condition causing macular edema is diabetes, the diagnosis becomes diabetic macular edema.

54. Diabetic macular edema is a severe complication of diabetic retinopathy and the most common form of vision impairment in individuals with diabetic retinopathy. EX1026 at 1. Diabetic macular edema, like poor perfusion or loss of perfusion of retinal capillaries from diabetes, also results from abnormal blood sugar levels causing damage to retinal capillaries that become leaky and result in swelling or edema, frequently causing symptoms of central vision loss when

occurring in the macula. EX2019 at 39-40. Diabetic macular edema may exist in the presence of non-proliferative or proliferative diabetic retinopathy.

B. Prior-Art Dosing Regimens Required Monthly or Individualized Dosing

55. In January 2011, the only anti-VEGF drug widely used and approved by the FDA for the treatment of an angiogenic eye disorder was ranibizumab, commercially known as “Lucentis”. EX1007 at 2. Although the anti-cancer drug bevacizumab (then commercially available as Avastin) was widely used off-label for treating wAMD, ranibizumab was by far the most extensively studied anti-VEGF drug for treating angiogenic eye disorders. *Id.* Macugen (pegaptanib) also was FDA approved for treatment of wAMD using an injection once every six weeks, EX2016, but was not widely used after the advent of more effective agents like Lucentis. It eventually was discontinued.

56. In both trials, called MARINA and ANCHOR respectively, patients in the experimental arms received monthly intravitreal injections of either 0.3 mg or 0.5 mg of ranibizumab for two years. *Id.*; EX2013 at 1-2. The results of MARINA and ANCHOR demonstrated that monthly intravitreal administration of ranibizumab reduced the risk of vision loss and increased the likelihood of vision gain, compared with no treatment (MARINA) or photodynamic therapy with verteporfin (ANCHOR). *Id.* at 2-3. After one year, fewer than 6% of the patients in the ranibizumab group lost 15 or more letters of vision (equivalent to 3 or more lines on

a standard eye chart where every 3 lines the size of the letters doubles in size) compared with more than 37% in the sham group. *Id.* FDA approved Lucentis for the treatment of wAMD in June 2006 with a label that recommended monthly dosing of 0.5 mg intravitreal injections. EX1029.

57. Unfortunately for patients, monthly injections also required monthly visits to doctors, imposing a substantial burden in terms of both time and financial resources. EX1007 at 2. Moreover, in my experience, many patients suffering from angiogenic eye disorders are older and/or vision impaired, and therefore require a family member or paid caregiver to accompany them. These monthly doctor's visits, which frequently require that patients travel long distances, thus impose extensive burdens on patients and those who support them. Frequent injections also come with elevated ocular risks of rare complications such as endophthalmitis, retinal detachment, and inflammation in the eye (uveitis). EX1025 at 4.

1. Extended, Fixed-Dosing Regimens Failed

58. The risks associated with frequent injections, as well as the financial and temporal burdens they impose on patients, prompted experiments with alternative dosing regimens to either reduce the number of injections or visits—sometimes both—without compromising visual acuity benefits. EX1007 at 2. For example, while one could decide to reduce the frequency of visits and injections to once a year, doing so would undoubtedly diminish the visual acuity benefits. The

challenge became finding an optimal dosing schedule that reduces the number of injections and/or visits and, at the same time, maintains visual acuity gains observed with monthly injections. EX2013 at 7.

59. The PIER study, which ran from August 2004 to March 2007, compared three monthly loading doses followed by fixed quarterly doses of 0.3 mg or 0.5 mg ranibizumab against a placebo control for over 24 months. EX2012 at 2. The clinical outcomes showed that while the treatment group gained visual acuity during the three initial monthly loading doses, their gains were lost when they transitioned to the fixed quarterly dosing period of the treatment regimen. *Id.* at 9. In fact, by the end of the year, both quarterly treatment groups had worse visual acuity than their baselines. *Id.* Moreover, at least as of October 2010, it became known that the patients treated quarterly also experienced a higher incidence of macular hemorrhage when compared with the control group receiving a placebo. EX2020 at 3, 7. The results were clearly inferior to the visual acuity gains observed in the phase III ranibizumab trials, MARINA and ANCHOR, in which patients received monthly injections of ranibizumab. EX2012 at 9; EX1025 at 4.

60. In fact, the PIER study sponsor amended the treatment protocol in August 2006 (i.e., the middle of the clinical trial) in order to allow *all* patients in the quarterly treatment arms to rollover and receive *monthly* injections of 0.5 mg ranibizumab through the remainder of the study. EX2012 at 2. In my experience as

a clinical investigator, protocol amendments that discontinue the originally planned regimen—the principal objective of the study—in the middle of a study typically are implemented only when there are serious safety or efficacy concerns with the drug or dosing regimen, warranting discontinuation of the experimental approach. The prior art summed up the state of affairs succinctly: “quarterly dosing is associated with poorer outcomes.” EX1007 at 2; *see also* EX1038 at 8 (“quarterly treatment is, on average, inferior to monthly treatment and that more frequent monitoring is needed.”).

61. The fact that quarterly dosing leads to worse outcomes was (and remains) reflected in Lucentis’s label. As I explained above, Lucentis’s label states that (for the treatment of wAMD), “LUCENTIS 0.5 mg (0.05 mL) is recommended to be administered by intravitreal injection once a month.” EX1029. The label goes on to explain that “[a]lthough less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared with continued monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be evaluated regularly.” *Id.* The label plainly teaches that fixed dosing at twelve weeks (every three months) leads to a “loss of visual acuity benefit” when compared with monthly injections of Lucentis, and the POSA thus would have read Lucentis’s label as consistent with the

prevailing clinical trial results guiding practitioners away from fixed, twelve-week dosing.

62. In my role as a key opinion leader, academic educator, clinical trialist, and clinician, I am familiar with, and have published on, how retinal specialists interpret study outcomes and apply them in their day-to-day practice. In my opinion, the POSA would have understood these clinical studies discussed above, and the prior art as a whole, to discourage the use of a fixed regimen in which patients transition from dosing every month directly to dosing once every twelve weeks, because the art suggested that fixed, twelve-week dosing regimens lead to worse clinical outcomes and/or vision loss.

63. In fact, in October 2009, I published an article in *Ophthalmology*, a leading journal in the field. There, I explained that the available study data allowed some comparison of monthly, quarterly, and PRN dosing regimens for ranibizumab, all of which tended to show that patients on a quarterly dosing schedule showed the worst clinical outcomes, and that—while dosing frequency can sometimes be reduced with a PRN dosing regimen—patients still may experience a reduction in visual acuity gains compared with patients on a monthly dosing regimen. EX2013 at 7.

64. In my opinion, the POSA in January 2011 would have believed fixed, twelve-week dosing regimens posed unacceptable risks of vision loss, including

permanent vision loss. Such treatment would have been inconsistent with the community standard of care, and doctors would have recommended against experimenting with such extended dosing regimen even under clinical trial settings at that time.

2. Some Physicians Used Individualized Dosing With Frequent Monitoring as an Alternative to Monthly Dosing

65. Although Lucentis was approved for monthly dosing, some doctors as of January 2011 (myself included) deviated from the labeled regimen and administered Lucentis (and/or Avastin) on an “as needed” basis—a regimen referred to as “pro re nata” or “PRN.” EX2013 at 7. Fundamentally, PRN regimens are individualized treatment regimens. When I decided to treat a patient PRN, I could not tell the patient ahead of time the frequency with which he or she would receive injections, because I simply did not know. Instead, I would ask the patient to return to my office at some defined interval (the length of which might vary by patient) so that I could assess the patient’s vision as well as certain physical characteristics of the patient’s eye (visual acuity, symptoms of vision loss) and retina (changes in retinal thickness on OCT imaging, new retinal hemorrhage from choroidal neovascularization (CNV), or worsening of the CNV lesion on fluorescein angiography). On the basis of those results, I would determine whether the patient

needed an immediate anti-VEGF injection or could go home without an injection and return later for another monitoring visit and another assessment.

66. Thus, for any given patient, after I had performed an assessment, determined that the patient needed an injection, and administered the injection, I could look backwards at that patient's previous treatment history to determine in hindsight how long it had been since the patient's last injection. But at that same moment, I would not be able to tell the patient how soon his or her next injection would take place. Thus, the PRN regimens I and other doctors used as of January 2011 differed from fixed regimens, because the frequency of future doses is not proscribed. Instead, dosing frequencies vary by patient and are up to the physician's discretion, exercised in conjunction with assessments that have not yet been performed, and at monitoring visits that have not yet taken place.

67. The frequency of monitoring visits in PRN regimens was up to a given doctor and patient. Many doctors brought patients in for monthly monitoring visits, others chose to monitor more or less frequently, and any given doctor might alter his or her monitoring frequency for any given patient at any given time based on their clinical discretion and the patient's presentation. EX1025 at 9 ("Retreatment should be based on each patient's clinical response and the frequency of monitoring should be tailored to each patient.").

68. In clinical trials, the protocol typically would specify the frequency of monitoring—some trials monitored monthly and some on other intervals. EX2021 at 6-7. Moreover, clinical trial protocols typically allowed patients a window of flexibility to schedule a visit around their target monitoring date, meaning that actual monitoring frequency could vary. EX2022 at 8 (clinicaltrials.gov entry for PrONTO study testing PRN dosing of ranibizumab, specifying monitoring visits of “every month [30±7 days]”). For example, if a patient in a trial with monthly monitoring visits was permitted a one-week window around a target visit date (e.g., the first of every month), the patient might come in for a first monitoring visit a week later than the target date but schedule the second monitoring visit a week earlier than the target date, resulting in an actual monitoring frequency (in that instance) of two weeks. If the patient then scheduled his or her third monitoring appointment precisely on the target date, the next monitoring interval would be five weeks. To this end, studies sometimes specify minimum treatment intervals that differ from the proposed monitoring frequency. EX2013 (explaining that SUSTAIN study testing PRN dosing for ranibizumab involved monthly monitoring); EX2017 at 9 (December 2010 Clinicaltrials.gov entry for SUSTAIN stating that “Ranibizumab was administered no sooner than 14 days after the previous treatment.”).

69. PRN regimens also were the subject of several clinical trials. For example, the PrONTO study evaluated the safety and efficacy of an as-needed, *pro*

re nata (PRN) dosing schedule for ranibizumab. EX1025 at 4-5. In the first three months, patients received monthly doses of ranibizumab, and for the remainder of the two-year study, doctors monitored patients monthly and assessed the need for further injections at each visit. *Id.* During these visits, the doctors used anatomic (qualitative OCT and evidence of new hemorrhage) and functional criteria (visual acuity gains) to guide their decisions. *Id.* The detailed criteria included recurrent choroidal neovascularization (creation of new blood vessels in the choroid layer of the eye) as evidenced by worsening vision, retinal thickening on OCT, and abnormalities on fluorescein angiogram (FA). EX1007 at 2. Regardless of patients' prior injection history, patients were required to visit their doctors monthly for individualized clinical assessment. *Id.* Unlike the fixed twelve-week dosing regimen, the PRN regimen achieved results comparable to those of the phase III clinical studies (MARINA and ANCHOR). EX1025 at 5. The results demonstrated that patients showed significant gains in visual acuity and decreases in retinal thickness. *Id.*

C. Clinical Studies for Aflibercept

70. Aflibercept (currently sold as Eylea[®]) is an anti-VEGF drug, first approved by the FDA for treating wAMD in November 2011. EX2010. Structurally, aflibercept is a fusion protein of key binding domains of human VEGFR-1 and -2 combined with a human IgG Fc fragment. EX1008 at 1.

71. Eylea[®] was approved based on two phase III clinical trials—VIEW 1 and VIEW 2. VIEW 1 and VIEW 2 studies shared the same design and dosing regimens, but VIEW 1 was conducted in the United States and Canada while VIEW 2 was conducted in Europe, Asia Pacific, Japan, and Latin America. EX1007 at 4. Patients enrolled in the VIEW 1 and VIEW 2 studies received either 0.5 or 2.0 mg of aflibercept at either 4-week or 8-week dosing intervals for the first year of the study. *Id.* In the second year, patients received PRN dosing with a capped interval—no more frequently than every four weeks and no less frequently than every 12 weeks. EX1018 at 6 (VIEW 2); EX1017 at 6-9 (VIEW 1). As I explain below, Fresenius and Dr. Galanis cite to several references describing the dosing regimens for VIEW 1 and VIEW 2, *see* EX1007; EX1017; EX1018; EX1022, but neither Fresenius nor Dr. Galanis identifies any prior art reference disclosing the results of VIEW 1 or VIEW 2 (such that the POSA would have understood that the trials were successful) nor any prior art data showing injection frequency in the second year (such that the POSA could have deduced, retrospectively, how frequently dosing in the PRN arm occurred).

D. Clinical Studies for Treating DME and DR Using Anti-VEGF Therapy

72. On February 18, 2010, Regeneron reported positive results in a phase 2 aflibercept study in patients with diabetic macular edema. EX1052 at 1. The study assigned patients to five groups. *Id.* The control group received macular laser

therapy, which was the standard of care at that time; two groups received monthly doses of 0.5 or 2.0 mg of aflibercept throughout the six months dosing period. *Id.* Two groups received three monthly doses of 2.0 mg of aflibercept (at baseline and weeks 4 and 8), followed through week 24 by either every 8-week dosing or as-needed (PRN) dosing with specific repeat dosing criteria. *Id.* Patients in each of the four dosing groups receiving VEGF Trap-Eye achieved statistically significantly greater mean improvements in visual acuity (8.5 to 11.4 letters of vision gained) compared with patients receiving macular laser therapy (2.5 letters gained) at week 24 ($p < 0.01$ for each VEGF Trap-Eye group versus laser). *Id.* The most gains in visual acuity were observed in patients who received 2 mg of initial three-monthly injections. *Id.*

73. During these clinical trials, none of the treatment arms used a fixed twelve-week dosing regimen. Instead, based on the information available at that time, the study design requiring monthly doses of aflibercept reflected doctors' concern that some patients may suffer visual acuity losses if they were not treated more frequently. While a small number of patients may require fewer doses than monthly injections, doctors cannot predict in advance which subset of patients will need fewer doses. Thus, doctors would not have expected a fixed, twelve-week dosing schedule to be successful, nor would they have been motivated to one due to

concerns that patients may experience a decline in visual acuity under that extended schedule.

VI. None of Dixon, NCT-377, NCT-795, Regeneron (8-May-2008) or Regeneron (18-Feb-2010) Discloses the 12-Week Regimen of the Challenged Claims

74. Dr. Galanis opines that each of Dixon (EX1007), NCT-377 (EX1018), NCT-795 (EX1017), and Regeneron (8-May-2008) (EX1022) discloses the dosing regimens claimed in 1-9 of the '345 patent. I disagree. For the reasons I explain below, it is my opinion that none of Dixon, NCT-377, NCT-795, or Regeneron (8-May-2008) disclose the limitation of claims 1-9 requiring that “each tertiary dose is administered 12 weeks after the immediately preceding dose.” For convenience below, I may refer to this limitation as the “12-week tertiary dosing” limitation.

75. Each of Dixon, NCT-377, NCT-795, or Regeneron (8-May-2008) describe the planned regimen for one of the two, materially identical phase III trials (VIEW 1 and VIEW 2) designed to test fixed, four-week dosing and fixed, eight-week dosing regimens of aflibercept in patients with wet AMD. EX1007; EX1017; EX1018; EX1022.

76. As I explained above, in each of VIEW 1 and VIEW 2, patients were assigned to one of four study arms for the first year of treatment: (1) “2.0 mg VEGF Trap-Eye administered every 8 weeks (including one additional 2.0 mg dose at Week 4);” (2) “0.5 mg VEGF Trap-Eye administered every 4 weeks,” (3) “2.0 mg VEGF

Trap-Eye administered every 4 weeks;” or (4) a control arm of “0.5 mg [of ranibizumab] administered every 4 weeks.” EX1018 at 6; EX1017 at 6-8; EX1007 at 3; EX1022 at 1. In the second year of the VIEW 1 and VIEW 2 studies, patients were to receive treatment PRN, with doses administered no more frequently than every four weeks and no less frequently than every 12 weeks. EX1018 at 6; EX 1017 at 6-8; EX1007 at 3; EX1022 at 1.

77. I understand Fresenius and Dr. Galanis assert that by disclosing a PRN regimen permitting doses somewhere between 4 and 12 weeks after the preceding dose, each of Dixon, NCT-377, NCT-795 and Regeneron (8-May-2008) discloses “one or more tertiary doses” “wherein each tertiary dose is administered 12 weeks after the immediately preceding dose.” Pet. at 46-47; EX1003 at 88, 110-111, 122. More specifically, I understand that Fresenius asserts that because each of Dixon, NCT-377, NCT-795 and Regeneron (8-May-2008) discloses a study designed with a first-year regimen that includes monthly-dosing arms followed by a second-year regimen of PRN dosing no more frequently than every four weeks and no less frequently than every twelve weeks, each reference thereby discloses a method of treatment involving a “tertiary” dose that is administered 12 weeks after the immediately preceding dose, where the preceding dose is the last monthly (“secondary”) dose of the first year. Pet. at 46-47.

78. I disagree. Simply put, that is not how the POSA would understand the disclosures of Dixon, NCT-377, NCT-795 or Regeneron (8-May-2008). The POSA would not understand an instruction to “administer the next dose when needed sometime between four and twelve weeks later” to mean the same thing as “administer the next dose twelve weeks later”. Nor would the POSA have any reason to expect that the first instruction would result in a dose administered at the same time as the second one.

79. In the same way, the POSA would not read the description of the VIEW trials’ second-year, PRN regimen in Dixon, NCT-377, NCT-795 or Regeneron (8-May-2008) to disclose a regimen in which the first dose of the second year was administered twelve weeks after the last dose of the first year. Instead, the POSA would understand these references to disclose that, for any given patient, the first dose of the second year of the study would and should be given whenever the patient happened to need it, sometime between four and twelve weeks after the last dose. This is particularly true where, as here, the references do not report the results of the regimen, or any data from which the POSA could understand when patients in fact required dosing during the PRN phase. I address the specific disclosures of each reference individually below.

A. Ground 1: Dixon Does Not Anticipate Challenged Claims 1-9 Because It Does Not Disclose the 12-Week Tertiary Dosing Limitation

80. Dixon is a scientific journal article titled “VEGF Trap-Eye³ for the treatment of neovascular age-related macular degeneration.” Dixon reviews “clinical trial data regarding VEGF Trap-Eye for the treatment of neovascular AMD.” EX1007 at 1-2. Regarding the phase III trials of aflibercept, Dixon states that:

A two part Phase III trial of VEGF Trap-Eye was initiated in August of 2007. The first part, VIEW 1 (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration) [46] will enroll - 1200 patients with neovascular AMD in the US and Canada. This non-inferiority 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), compared with 0.5 mg of ranibizumab

³ In his declaration, Dr. Galanis opines that “VEGF Trap-Eye” refers to aflibercept, and that VEGF Trap-Eye, as disclosed in Dixon, NCT-377, NCT-795 and Regeneron (8-May-2008), satisfy the claim limitation “wherein the VEGF antagonist is a receptor-based chimeric molecule comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor which is Flt1 and Ig domain 3 of a second VEGF receptor which is Flk1, and a multimerizing component.” EX1003 at 91-92, 113-14, 124-25. For the purpose of this declaration, I have been instructed to assume that Dixon’s disclosure of VEGF Trap-Eye is a disclosure of aflibercept.

administered every 4 weeks. After the first year of the study, patients will enter a second year of p.r.n. dosing evaluation. The VIEW 2 [47] study has a similar study design and is currently enrolling patients in Europe, Asia Pacific, Japan and Latin America. In both trials, the primary outcome will be the proportion of patients who maintain vision at week 52 (defined as a loss of < 15 ETDRS letters).

Id. at 4.

81. Neither Fresenius in the Petition nor Dr. Galanis in his declaration suggests that the above language discloses the 12-week tertiary dosing limitation. However, I understand that Fresenius and Dr. Galanis assert that, as a legal matter, Dixon should be interpreted to contain the disclosure of NCT-377 because Dixon “incorporates by reference” NCT-377. I have not been asked to form an opinion relating to whether or not this incorporation by reference theory is correct or appropriate. Instead, I have been asked to assume for the sake of this declaration that Dixon *does* incorporate by reference NCT-377.

82. Nevertheless, and as I explain below, *infra* Section VI.B, it is my opinion that NCT-377 does not disclose the claimed 12-week tertiary dosing limitation. Thus, even assuming that Dixon incorporates NCT-377 by reference, it is my opinion that such incorporation does not cure Dixon’s failure to disclose the claimed 12-week tertiary dosing limitation. I therefore conclude that Dixon does not

anticipate challenged claims 1-9 as Fresenius asserts in Ground 1, because Dixon does not disclose every element of the challenged claims as arranged in the claim.

B. Ground 2: NCT-377 Does Not Anticipate Challenged Claims 1-9 Because It Does Not Disclose the 12-Week Tertiary Dosing Limitation

83. Dr. Galanis asserts that NCT-377 (EX1018) is an online record from the clinicaltrials.gov website. EX1003 at 56. Clinicaltrials.gov is an online database of clinical research studies that is updated over time as new information about the study (or its results) becomes available. *Id.* NCT-006373777 (“NCT-377”) is the identifier for the VIEW 2 study, entitled “VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [Age-Related Macular Degeneration] (VIEW 2).” EX1018 at 1.

84. Dr. Galanis states that for purposes of forming his opinion, he relies on the August 4, 2008, entry for NCT-377. EX1003 at 56-57, 66. However, I observe that EX1018 does not appear to be the August 4, 2008, entry for NCT-377. *See* EX1018 at 1, 3. I do not know whether Dr. Galanis reviewed or relied on something other than EX1018 in the course of forming his opinions nor have I attempted to compare one version or another of the clinicaltrials.gov entries for NCT-377. For purposes of my opinions, I was instructed to analyze the disclosure of EX1018 as it was submitted in this proceeding.

85. NCT-377 discloses the following protocol for VIEW 2:

- Arm 1: “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.” EX1018 at 6.
- Arm 2: “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.” *Id.*
- Arm 3: “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.” *Id.*
- Arm 4: “0.5 mg [of ranibizumab] 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.” *Id.*

86. Dr. Galanis opines that among the four dosing regimens disclosed in NCT-377, the dosing regimens used in experimental arms 2 and 3 satisfy all limitations of challenged claims 1-9. EX1003 at 85. With respect to the 12-week tertiary dosing limitation, Dr. Galanis relies on the statement in NCT-377, in both arms 2 and 3, that “dose[s] may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” as showing that doses “can, in fact, be as infrequent as every 12 weeks, including 12 weeks after the final 0.5 or 2.0 mg

‘secondary dose’ at the end of the first year.” EX1003 at 88. Dr. Galanis provides no further context for why he believes the quoted language is a disclosure of the 12-week dosing limitation.

87. For all the reasons I explained above, I disagree that the statement “dose[s] may be administered as frequently as every 4 weeks, but no less frequently than every 12 weeks” in the second year of a study discloses a regimen in which a dose is administered 12 weeks after the last (monthly) dose of the first year of the study. Instead, the POSA would understand this statement to disclose a dose administered *as soon as a physician decided one was necessary*, sometime between four and twelve weeks after the last dose at the end of the first year of the study. In my experience, physicians do not interpret “dose as needed, but no sooner than four weeks and no later than 12 weeks after the last dose” to mean “dose 12 weeks after the last dose.” Such an interpretation would run counter to clinical practice and experience. EX1007 at 2; EX1038 at 8; EX1025 at 2.

88. NCT-377 does not disclose how physicians should decide when to administer an injection at any given time within the four-to-twelve-week window NCT-377 describes. EX1018. Nor does NCT-377 disclose how frequently physicians should assess a patient for retreatment. *Id.* Nor does NCT-377 disclose any results from VIEW 2 that would allow the POSA to determine whether a patient in either of arms 2 or 3 *in fact* received a dose twelve weeks after their last monthly

dose in the first year. *Id.* Instead, NCT-377 discloses only that patients were not *prohibited* from receiving a dose on that schedule. *Id.* As I explained above, *supra* Section V.B.2, the frequency of monitoring visits (as well as the scheduling “grace” window afforded patients around the target monitoring date) varies by clinical trial, meaning that the number of *possible* injection intervals is vast.

89. Nor, in my opinion, would the POSA understand NCT-377 to mean that the 12-week tertiary dosing limitation necessarily was present. To the contrary, the disclosure of NCT-377 describes a trial that merely permits the *possibility* of a tertiary dose administered 12 weeks after the last monthly one. Dr. Galanis seems to agree. On the basis of NCT-377, he asserts only that tertiary doses “can be as infrequent as every 12 weeks”, EX1003 at ¶ 88 (emphasis added). The Petition is no less speculative, and states that tertiary doses “may be administered as infrequently as 12 weeks after the immediately preceding dose.” Pet. at 46-47 (emphasis added).

90. Because I conclude that NCT-377 does not disclose the 12-week dosing limitation present in each one of challenged claims 1-9, it is my opinion that NCT-377 does not anticipate challenged claims 1-9, as Fresenius asserts in Ground 2.

C. Ground 3: NCT-795 Does Not Anticipate Challenged Claims 1-9 Because It Does Not Disclose the 12-Week Tertiary Dosing Limitation

91. Dr. Galanis asserts that “NCT-795 is an online record for the VIEW 1 clinical trial NCT-00509795 from the clinicaltrials.gov [s]ite.” EX1003 at 51. NCT-0000509795 (“NCT-795”) is the identifier for the VIEW 1 study, entitled “VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 1).” EX1017 at 1.

92. Dr. Galanis asserts that “[i]n coming to [his] opinions in this case, [he] relied on Version 9, which was published April 28, 2009.” EX1003 at 54. I note that EX1017 appears to be a comparison of two different versions of NCT-795 study records. I do not know whether Dr. Galanis reviewed or relied on something other than EX1017 in the course of forming his opinions nor have I compared one version or another of the clinicaltrials.gov entries for NCT-795. For purposes of my opinions, however, I was instructed to analyze the disclosure of EX1017 as it was submitted in this proceeding.

93. EX1017 discloses the following about the VIEW 1 dosing protocol in green highlighting (which is what I understand Dr. Galanis to rely upon, as opposed to the crossed-out red text below the green highlighting):

- Arm 1: “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.” EX1017 at 8.

- Arm 2: “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.” *Id.* at 6.
- Arm 3: “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.” *Id.* at 7.
- Arm 4: “0.5 mg [of ranibizumab] 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.” *Id.* at 8.

94. The disclosure recited above is identical to the relevant disclosure in EX1018. Thus, it is my opinion that NCT-795 fails to disclose the 12-week tertiary dosing limitation of challenged claims 1-9 for all the reasons stated above with respect to NCT-377. *Supra* Section VI.B. I therefore conclude that NCT-795 does not anticipate challenged claims 1-9, as Fresenius asserts in Ground 3.

D. Ground 4: Regeneron (8-May-2008) Does Not Anticipate Challenged Claims 1-9 Because It Does Not Disclose the 12-Week Tertiary Dosing Limitation

95. Regeneron (8-May-2008) is a document entitled “Bayer and Regeneron Dose First Patient in Second Phase 3 Study for VEGF Trap-Eye in Wet Age Related

Macular Degeneration.” EX1022. Regeneron (8-May-2008) discloses the dosing protocol for the VIEW 2 study as follows:

In the first year, 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 doses of 0.5 milligrams (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 four. Patients randomized to the ranibizumab arm of the trial will receive a 0.5 mg dose every 4 weeks. After 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 until the end of the study.

EX1022 at 1.

96. Similar to their arguments with respect to Dixon, NCT-377, and NCT-795, Fresenius and Dr. Galanis assert that Regeneron (8-May-2008) discloses the 12-week tertiary dosing limitation by virtue of its description of the second year of the VIEW 2 trial—i.e., “After 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 until the end of the study.” *Id.*

97. The POSA would understand the reference to a “flexible, criteria-based extended regimen with a dose administered at least every 12 weeks, but not more

often than every four weeks” to refer to dosing *as needed* based on physician assessments to be conducted in the future. Regeneron (8-May-2008) does not specify the criteria physicians should use for retreatment, nor does it specify the frequency with which they should conduct such treatments. As I explained above, *supra* Section V.B.2, the frequency of monitoring visits (as well as the scheduling “grace” window afforded patients around the target monitoring date) varies by clinical trial, meaning that the number of *possible* injection intervals is vast. Thus, and for all the reasons I described above with respect to Dixon, NCT-377, and NCT-795 (which I incorporate by reference here), the POSA would not understand this disclosure of an individualized, as-needed regimen *permitting* doses *any time between four and twelve weeks* to disclose a regimen in which a patient who had previously received monthly doses would immediately switch to a twelve-week interval.

98. Nor, in my opinion, would the POSA understand Regeneron (8-May-2008) to mean that the 12-week tertiary dosing limitation necessarily was present. To the contrary, the disclosure of Regeneron (8-May-2008) describes a trial design that merely permits the *possibility* of a tertiary dose administered 12 weeks after the last monthly one. Again, Dr. Galanis seems to agree. On the basis of Regeneron (8-May-2008), he asserts only that tertiary doses “can be as infrequent as every 12 weeks”, EX1003 at ¶ 292 (emphasis added). The Petition is no less speculative, and

states that tertiary doses “may be administered as infrequently as 12 weeks after the immediately preceding dose.” Pet. at 46-47 (emphasis added).

E. Ground 5: Claims 1-9 Are Not Obvious Over Dixon In View of NCT-377

99. Dr. Galanis opines that, in the event it is determined that Dixon does not properly incorporate NCT-377 by reference, challenged claims 1-9 nevertheless would have been obvious over Dixon in view of NCT-377. I disagree for several reasons.

100. First, as I explained above, it is my opinion that *neither* Dixon nor NCT-377 discloses the claimed 12-week tertiary dosing limitation. *Supra* Sections VI.A and VI.B. Thus, it would not matter whether the POSA examined their disclosures together or separately, because nothing in *either* Dixon or NCT-377 would point the POSA toward a 12-week dosing regimen.

101. Furthermore, and as I set forth above in the legal standards section of my declaration, I understand from counsel that in order to establish that an invention would have been obvious to the POSA, one must demonstrate that the POSA would have had reason to combine the selected portions of the identified references in a manner that would lead to the claimed invention, and that the POSA would have had a reasonable expectation that doing so would prove successful. *Supra* Section III. Dr. Galanis did not address either point—the only assertion I see in his declaration relevant to Ground 5 is in paragraph 205: “And alternatively, the Challenged Claims

are obvious over Dixon in view of NCT-377.” Thus, I do not know why Dr. Galanis concludes that the POSA would have had a reason to combine Dixon and NCT-377 to arrive at the inventions of the challenged claims, all with a reasonable expectation of success.

102. Regardless, having considered the prior art, I do not believe that the POSA *would* have had a reason to combine Dixon with NCT-377 in a manner that led to the claimed inventions, including because Dixon itself teaches away from those inventions when it states that “quarterly dosing is associated with poorer outcomes.” EX1007 at 2. This disclosure would *not* have encouraged the POSA to modify Dixon’s teachings to incorporate a quarterly dosing component; it would have done the opposite, because wAMD is a serious disease where, if patients are undertreated, they could suffer serious long-term consequences such as retinal detachment and permanent vision loss. To that end, neither Dixon nor NCT-377 (nor any other reference Dr. Galanis relies on as prior art) discloses the results of VIEW 1 or VIEW 2.⁴ Thus, the POSA would not even have known whether

⁴ Dr. Galanis does cite to Heier-2012 (EX1031), which reports the VIEW 1 and VIEW 2 results, but Dr. Galanis does not include Heier-2012 within the “Scope of Prior Art”, Ex. 1003 § X, presumably due to its date of publication, which is in 2012 and thus after the priority date of the ’345 patent (discussed *supra* Section IV.A).

aflibercept was in fact safe and effective on a *shorter* dosing interval, let alone been encouraged to pursue the longer, quarterly interval of the challenged claims.

103. Accordingly, it is my opinion that challenged claims 1-9 would not have been obvious to the POSA in view of Dixon in combination with NCT-377. In the event trial is instituted, I expect to explain my opinions regarding the nonobviousness of the claimed methods in more detail.

F. Grounds 6-9: Claims 10-11 Are Not Obvious Over NCT-795, NCT-377, and Dixon, in View of Regeneron (18-Feb-2010) And “A POSA’s Knowledge”

104. Challenged claims 10 and 11 recite methods of treating DR and DME, respectively. They also depend on challenged claim 1 and therefore require one or more tertiary doses administered 12 weeks after the immediately preceding dose. Fresenius and Dr. Galanis argue with respect to each of Grounds 6-9 that the POSA would have been motivated to combine the 12-week tertiary dosing (allegedly) disclosed in one of Dixon, NCT-377, NCT-795, or Regeneron (8-May-2008) with Regeneron (18-Feb-2010) and “a POSA’s knowledge.” Pet at 52-56. I disagree.

105. First, for all the reasons explained above in Sections VI.A to VI.D, I disagree with a core premise of Dr. Galanis’s theory of obviousness. Namely, I disagree that any of Dixon, NCT-377, NCT-795, or Regeneron (8-May-2008) in fact discloses the 12-week tertiary dosing limitation for the treatment of wAMD. Because that premise fails, so too does Dr. Galanis’s obviousness assertions.

106. Furthermore, as I addressed briefly with respect to Dixon in Section VI.E, and more generally in Section V.B.1 above, the prior art would have taught the POSA away from the use of quarterly dosing. For example, Dixon itself states that “quarterly dosing is associated with poorer outcomes,” EX1007 at 2, and Mitchell explains that “quarterly treatment is, on average, inferior to monthly treatment and . . . more frequent monitoring is needed.” EX1038 at 8. These prior art statements would have steered the POSA in a direction away from the claimed invention, because DME and DR are serious diseases that can lead to long-term irreversible vision problems if untreated or undertreated.

107. In addition, I understand Regeneron contends that Fresenius has not established whether Regeneron (18-Feb-2010) is prior art. For purposes of this declaration, I have assumed Regeneron (18-Feb-2010) is part of the prior art, but my ultimate opinion that challenged claims 10-11 are not invalid for obviousness would be the same regardless of Regeneron (18-Feb 2010)’s status as prior art.

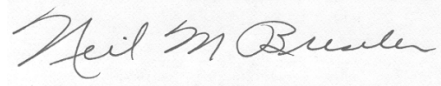
108. I therefore conclude that challenged claims 1-9 would not have been obvious to the POSA in view of Dixon in combination with NCT-377. In the event trial is instituted, I expect to explain my opinions regarding the nonobviousness of the claimed methods in more detail.

VII. CONCLUSION

109. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on October 23, 2025

Signature: _____

A handwritten signature in cursive script, appearing to read "Neil M. Bessler", is written on a light gray rectangular background.