

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.
Patent Owner.

Patent No. 11,253,572

Inter Partes Review No. IPR2023-00884

DECLARATION OF DAVID M. BROWN, M.D.

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I, David M. Brown, M.D., declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Patent Owner, Regeneron Pharmaceuticals, Inc., as a technical expert in connection with the *Inter Partes* Review proceeding identified above. I submit this declaration in support of Regeneron's Response in this proceeding.

2. I understand that Petitioner Samsung Bioepis Co., Ltd. challenges a number of claims of United States Patent No. 11,253,572 ("the '572 Patent") in this proceeding.

3. I understand that Petitioner has asserted Shams (Ex.1017), a Genentech patent application filed in 2004, as one of its prior art references. The Shams reference focuses on the protocol for Genentech's PIER trial. I was a principal investigator on PIER, and so I have been asked to opine on aspects of PIER that could color a POSA's understanding of the Shams reference.

4. I understand that Petitioner has asserted the 2010 ARVO Abstract (Ex.1010) reporting certain top-line results of the DA VINCI trial. I was a clinical investigator on the DA VINCI trial, so I have been asked to explain my and the other clinical investigators' role on the DA VINCI trial. I am also listed with Dr. James Major as one of the authors on the 2010 ARVO Abstract, so I have been asked to explain my and Dr. Major's roles in preparing the abstract.

5. I have personal knowledge of Exhibits 2022–2023 and 2077–2080 cited in this declaration, which are true and correct copies of documents I received, sent, or reviewed.

6. I am being paid my usual hourly rate for my work on this matter. I have no personal or financial stake or interest in the outcome of the present proceeding.

II. QUALIFICATIONS

7. I am the Director of the Greater Houston Retina Research Center, where I have been a Physician Partner and Researcher since 1995. I also have a series of academic appointments: Clinical Professor of Ophthalmology, Cullen Eye Institute at Baylor College of Medicine; Vice-Chair of Ophthalmology for Research and Associate Clinical Professor of Ophthalmology at the Methodist Hospital, Weill Cornell College of Medicine in Houston, Texas; and the NASA Research and Clinical Advisory Panel—Space Associated Neuro-Ophthalmic Syndrome at NASA Johnson Space Center in Houston, Texas.

8. I graduated from Baylor College of Medicine with highest honors in 1988. I completed a medical/surgical internship at Baylor College of Medicine from 1989 to 1990. From 1990 to 1995, I completed ophthalmology and retina training at the University of Iowa, where I was a Thomas Heed Fellow and a Hermann Knapp Fellow, and was awarded the Ron Michels Fellowship award presented to the top retinal surgery fellow in the United States in 1994.

9. I have served on the Board of Directors of the American Society of Retina Specialists since 2014; the Macula Society Credentials Committee since 2013; and the Retina Society Finance Committee since 2018. I have served in numerous additional leadership roles in professional organizations and societies in the retina and ophthalmology field over the past three decades. I have also been a peer reviewer for the journals in these fields, including *Ophthalmology*, *Retina*, and the *New England Journal of Medicine*.

10. I maintain an active medical and surgical practice focused on treatment of retinal diseases and have continuously been elected as one of the “Best Doctors in America” from 2007 to 2024 and “Texas Super Docs” from 2009 to 2024. I am also an elected member of the Macula Society, the Retina Society, and the Club Jules Gonin. My honors include the American Academy of Ophthalmology Honor Award (2000), the American Society of Retina Specialists Honor Award (2008), the ASRS Senior Honor Award (2010), the AAO Senior Honor Award (2014), and Retina Hall of Fame inaugural inductee (2017).

11. My research and clinical trial experience has led to my recognition as an international thought leader on treatments and current standards of care for age-related macular degeneration, retinal vein occlusion, and diabetic retinopathy. I have written and published over 400 national meeting presentations, abstracts, and scientific papers, including many of the primary papers establishing the safety and

efficacy of use of anti-vascular endothelial growth factor (anti-VEGF) agents for angiogenic eye disorders, including wet age-related macular degeneration (wAMD), diabetic macular edema (DME), and diabetic retinopathy (DR).

12. I have served as an investigator on Phase III clinical trials of anti-VEGF agents ranibizumab (Genentech's Lucentis) and aflibercept (Regeneron's Eylea) in wAMD, DME, and DR. For example, I was an investigator on:

- Genentech's ANCHOR and MARINA trials, phase III trials of ranibizumab patients with AMD;
- Genentech's PIER trial, a phase IIIb trial of ranibizumab in patients with AMD;
- Genentech's RISE and RIDE trials, phase III trials of ranibizumab in patients with DME;
- Regeneron's VIEW1 trial, a phase III trial of aflibercept in patients with AMD; and
- Regeneron's PANORAMA trial, a phase III trial of aflibercept in patients with DR without center involved DME.

My research efforts have contributed to a transformation in the nature of treatments and outcomes for angiogenic eye disorders. A current copy of my curriculum vitae is filed herewith as Ex.2081.

III. MATERIALS CONSIDERED

13. In preparing this declaration, I have reviewed, among other things, the following materials:

- The Petition for *Inter Partes* Review of the '572 Patent, Paper 2 (“Petition”);
- The Declaration of Dr. Edward Chaum (Ex.1002) (“Chaum Declaration”);
- The Board’s Decision Granting Institution of *Inter Partes* Review, Paper 13; and
- All exhibits cited in this declaration.

IV. THE ANCHOR, MARINA, AND PIER TRIALS

14. I understand that the parties dispute the priority date of claim 25 of the '572 Patent. I have been asked by counsel to assume that the priority date for this claim is January 13, 2011, and to discuss the art as it was understood before that date. My opinions would not change if the priority date were instead July 12, 2013.

A. ANCHOR and MARINA: Trials establishing effectiveness of monthly ranibizumab

15. In 2003, Genentech began two large-scale, randomized Phase III clinical trials to test monthly ranibizumab injections in subjects with wAMD—

MARINA and ANCHOR. I served as a principal investigator for both studies. Ex.2082¹ (ANCHOR); Ex.2083² (MARINA).

16. MARINA ran from March 2003 to December 2005. 716 subjects with wAMD, with either minimally classic or occult choroidal neovascularization (CNV), were randomly assigned to receive 24 monthly intravitreal injections of Lucentis (either 0.3 mg or 0.5 mg) or sham injections. Ex.2083 (MARINA) at 2–3. The primary endpoint of the study was the proportion of subjects losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.* at 2.

17. The one-year results of MARINA, presented in July 2005, showed that nearly 95% of subjects treated with Lucentis® maintained or improved vision at 12 months. Ex.2084 at 4. The two-year results, published in October 2006, showed that the mean improvements in vision demonstrated in the first 12 months of the study were sustained through the second year of study. Ex.2083 (MARINA) at 11. Mean increases in visual acuity were +6.5 letters in the 0.3 mg group and +7.2 letters

¹ David M. Brown et al., *Ranibizumab Versus Verteporfin for Neovascular Age-Related Macular Degeneration*, 355 N. ENG. J. MED. 1432 (2006).

² Philip J. Rosenfeld, David M. Brown et al., *Ranibizumab for Neovascular Age-Related Macular Degeneration*, 355 N. ENG. J. MED. 1419 (2006).

in the 0.5 mg groups, compared with a decrease of -10.5 letters in the sham-injection group. Ex.2084³ (Dec. 30, 2005, Genentech Press Release) at 4.

18. The unmasking of the one-year results of the MARINA study prompted discussion with the data and safety monitoring committee, and it was determined in October 2005, two months before the end of the patient's final study visit at 24 months, that all subjects still in the sham arm could be offered ranibizumab injections. Monthly ranibizumab injections were determined by this point to be a critical tool to not only arrest vision loss in wAMD patients, but to offer hope for sustained improvements in visual acuity.

19. The MARINA results were supplemented by the outcomes from the ANCHOR trial. ANCHOR ran from May 2003 to September 2006 and enrolled 423 subjects with predominantly classic choroidal neovascularization in wAMD. Ex.2082 (ANCHOR) at 1. Study subjects were randomized to receive monthly intravitreal Lucentis (0.3 mg or 0.5 mg) plus sham photodynamic verteporfin therapy or monthly sham injections plus active verteporfin therapy. *Id.* As in MARINA, the

³ Press Release, *Genentech, Inc. Submits Biologics License Application for FDA Review of Lucentis(TM) in Wet Age-Related Macular Degeneration* (Dec. 30, 2005), <https://www.biospace.com/article/releases/genentech-inc-submits-biologics-license-application-for-fda-review-of-lucentis-tm-in-wet-age-related-macular-degeneration-/>.

primary endpoint of the study was also the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months. *Id.*

20. One-year results of the ANCHOR trial, presented in November of 2005, showed that 94–96% of those treated with 0.5 mg of Lucentis maintained or improved vision compared to approximately 64% of those treated with photodynamic therapy (PDT) alone. Ex.2084 (Dec. 30, 2005, Genentech Press Release) at 2–3. The two-year results, published in January 2009 showed visual acuity improved from baseline, on average, by +8.1 to +10.7 letters, versus a mean decline of -9.8 letters in the verteporfin photodynamic group. Ex.1049⁴ at 1.

21. ANCHOR, while confirming the effectiveness of a monthly intravitreal ranibizumab treatment regimen, also represented a “major breakthrough in the treatment of predominantly classic CNV secondary to AMD” by showing this treatment was “superior to verteporfin PDT” treatment. Ex.1049 (ANCHOR 2009) at 7. “The VA benefit from ranibizumab was both rapid and sustained: The superiority of ranibizumab to PDT was evident by 1 month after starting treatment, increased to a plateau by the end of the first year, and then persisted through month 24.” *Id.* Like the MARINA study, the positive results demonstrated in the

⁴ David M. Brown et al., *Ranibizumab Versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study*, 116 OPTHALMOLOGY 57 (2009).

ranibizumab treatment arms resulted in a protocol amendment that allowed subjects in the PDT-alone arm of the study to cross over to ranibizumab injections during the latter part of the study. *Id.* at 4.

B. PIER and other trials testing less frequent ranibizumab

22. After ANCHOR and MARINA, Genentech also conducted a number of studies with Lucentis in an effort to explore less frequent dosing, including SUSTAIN, EXCITE, PrONTO, SAILOR, and PIER. Each of these prior art studies with Lucentis demonstrated inferior results to the fixed monthly dosing regimen of ANCHOR and MARINA.

23. In 2004, Genentech initiated the PIER Study, which ran from August 2004 to March 2007, and was designed to compare three monthly loading doses followed by fixed quarterly dosing of 0.3 mg and 0.5 mg Lucentis against sham control over 24 months in 184 patients. Ex.1021 at 2, 4.⁵ I participated as a clinical investigator, was part of the PIER Study Group, and was also involved in the presentation and publication of the Year One data from PIER. As explained below, the PIER Study revealed that fixed quarterly intravitreal injections of

⁵ Carl D. Regillo, David M. Brown et al., *Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 1*, 145 AM. J. OPHTHALMOLOGY 239 (2008).

ranibizumab over an extended treatment period was not an effective method of treatment.

24. From the results of the MARINA and ANCHOR trials and my experience administering monthly ranibizumab as part of those trials, I knew that monthly ranibizumab could improve AMD relatively quickly, with a majority of the visual gain achieved within the first three months. After this initial improvement, I and other PIER investigators did not expect symptoms to recur quickly, and so we thought that a longer dosing interval could work to prevent AMD symptoms from recurring. I thought it would be feasible to find a longer dosing interval that would maintain at least some of the initial vision gains, and I thought the PIER dosing schedule was likely to work for this purpose.

25. As one of the lead clinical investigators on the PIER trial, I received the first read-out of the one-year data from the study from Genentech in early 2006 and was the first to present on this data at the Retinal Physician Symposium held in the Bahamas from May 31 to June 3, 2006. The data was highly disappointing to say the least. While patients saw an initial gain in visual acuity during the three-monthly loading doses, these gains were entirely lost once quarterly dosing began. Ex.1021 (PIER 2008) at 7 (“On average, there was 4.5-letter decline in VA between month three and month 12 for both ranibizumab dose groups.”). By month 12, the 0.3 mg

study arm saw a -1.6 letter difference from baseline visual acuity, and the 0.5 mg study arm saw a -0.2 letter difference from baseline. *Id.* at 5 fig.1.

26. Optical coherence tomography (OCT) assessed anatomic outcomes in the Year One data also confirmed ranibizumab's failure to maintain efficacy over the quarterly dosing period. The maximal decrease in foveal center point thickness was seen at months two and three for both ranibizumab groups. Ex.1021 (PIER 2008) at 7. During assessments made at months five and eight, the foveal center point thickness was on average greater than at months two and three, and was also greater than at month 12, which had followed a ranibizumab dose at month 11. *Id.* This suggested that, on average, ranibizumab's therapeutic effectiveness in a patient would wane between injections, pointing to recurrent neovascular activity and associated exudation occurring between injections. Ex.2085⁶ at 4.

27. Over the course of the PIER study, the study sponsor (Genentech) implemented two key protocol amendments. First, the protocol was amended on February 27, 2006, to provide sham injection patients the opportunity to cross over to receive 0.5 mg ranibizumab quarterly after completing the month-12 visit (*i.e.*,

⁶ Jonathan P. Levine et al., *Macular Hemorrhage in Neovascular Age-Related Macular Degeneration After Stabilization with Antiangiogenic Therapy*, 29 RETINA 1074 (2009).

the assessment time point for the primary analysis). Ex.2051⁷ at 2. As explained above, the 12-month data from MARINA and ANCHOR had established to the retinal community that it would be in the best interest of subjects in the sham cohorts to be treated with ranibizumab, rather than be put further at risk for severe, irreversible vision loss under an observation-only or PDT scheme.

28. The second protocol amendment was the direct result of the review of the 12-month PIER data and the disappointing lack of efficacy of subjects in the treatment arms. On August 21, 2006, the study was amended to provide all patients remaining in the study the opportunity to roll over to receive 0.5 mg ranibizumab monthly for the remainder of the study. Ex.2051 (Abraham 2010) at 2. The second year of the PIER study was functionally designed to be confirmatory of fixed quarterly dosing's efficacy and, given the disappointing lack of efficacy observed in the PIER quarterly treatment regimen, the study sponsor initiated a rollover at this point to mitigate against future visual acuity losses, which would be expected on continued quarterly dosing.

29. The year-two results from PIER confirmed the disappointing lack of efficacy of the dosing regimen. The 0.3 mg ranibizumab group saw a mean loss

⁷ Prema Abraham et al., *Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2*, 150 AM. J. OPHTHALMOLOGY 315 (2010).

of -2.2 letters as compared to baseline, and the 0.5 mg ranibizumab arm saw a mean loss of -2.3 letters as compared to baseline. Ex.2051 (Abraham 2010) at 5 tbl.3. This stood in stark contrast to MARINA and ANCHOR. *Id.* at 8 (“In those studies, patients who received monthly injections of ranibizumab experienced a gain of 5 to 11 letters from baseline at month 24 compared to a loss of approximately 2 letters with the PIER dosing regimen.”). After approval of Lucentis, and certainly by 2011, the goal of any treatment regimen for age-related macular degeneration was to improve vision, maintain those gains, and prevent blindness.

30. Post-hoc analyses of the study data from MARINA, ANCHOR, and PIER also demonstrated that while patients on monthly ranibizumab were significantly less likely to develop macular hemorrhages as compared to sham control, patients in the treatment arm of PIER saw no benefit in the incidence of macular hemorrhage as compared to sham control and, indeed, incidence rates were numerically higher. Ex.2086⁸ at 3, 7.

31. Importantly, macular hemorrhages are a hallmark of active wAMD and are considered to be a definitive sign of disease progression. “[W]hen occupying larger areas or located in the subfoveal region, they are usually associated with a

⁸ Irene Barbazetto et al., *Dosing Regimen and the Frequency of Macular Hemorrhages in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab*, 30 RETINA 1376 (2010).

poor visual prognosis in a majority of cases.” Ex.2086 (Barbazetto 2010) at 1. It was a serious concern, therefore, that quarterly dosing did not decrease the incidence of macular hemorrhage as compared to sham and it was recognized that “switching from monthly to quarterly injection intervals may not have the same beneficial effect and could put the patient at an increased risk for vision-threatening complications.” *Id.* at 9.

32. As a result, my conclusion from the PIER Study results was that “we cannot just mandatorily treat on a quarterly basis and maintain the visual gains seen with the first three monthly injections.” Ex.2087⁹ at 1, 2 (“You can’t just do mandatory quarterly injections.”). My expressed concerns with fixed quarterly injections were shared across the retina community at the time. *E.g.*, Ex.2085 (Levine 2009) at 4–5 (“A recent analysis of the ANCHOR, MARINA, and PIER data demonstrated that monthly intravitreal ranibizumab dosing significantly reduced the frequency of macular hemorrhages compared with the sham controls or photodynamic therapy-treated patients regardless of lesion type. ***The effect was lost when patients were switched from monthly to quarterly dosing in the PIER study.***”).

⁹ Daniele Cruz, *PIER Data Suggest a Need for Tailored Injection Schedule*, OCULAR SURGERY NEWS (Sept. 1, 2006), <https://www.healio.com/news/ophthalmology/20120331/pier-data-suggest-a-need-for-tailored-injection-schedule>.

Reducing the frequency of injections should, therefore, be done with caution.”)

(emphasis added).

33. At the outset of the PIER trial, I had no reason to think visual acuity outcomes in the quarterly dosing arm would fall so far short of the outcomes in the monthly dosing arm. The results of the PIER trial showed it was more challenging than I had thought it would be to find a fixed extended dosing regimen that could still effectively treat AMD and other angiogenic eye disorders. Others shared this view. Based on the PIER data, Genentech “recommend[ed] that patients receive either monthly injections of ranibizumab, or have their retreatment schedules determined through individualized testing.” Ex.2050¹⁰ at 2.

34. These concerns were also reflected in the FDA’s labeling when Lucentis was approved for wAMD treatment in June 2006, as PIER’s year-one results were included in the FDA’s review. Ex.2088¹¹ (Genentech June 30, 2006, press release) at 2. The label explains: “Although less effective, treatment may be reduced to one injection every three months after the first four injections if monthly injections are not feasible. Compared to continued monthly dosing, dosing every

¹⁰ *Retinal Physician Symposium Covers Broad Range of Topics*, RETINAL PHYSICIAN (Sept. 1, 2006), <https://www.retinalphysician.com/issues/2006/september-2006/retinal-physician-symposium-covers-broad-range-of>.

¹¹ Press Release, Genentech, *FDA Approves Lucentis for the Treatment of Wet Age-Related Macular Degeneration* (June 30, 2006).

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.” Ex.2089¹² at 2.

V. THE DA VINCI TRIAL AND 2010 ARVO ABSTRACT

35. The DA VINCI trial was a phase II trial of VEGF Trap-Eye in subjects with DME. Ex.2014, 2. Patients were enrolled between December 2008 and June 2009. *Id.* The primary endpoint was change in Best-Corrected Visual Acuity at 24 weeks. *Id.* Although Regeneron and Bayer collaborated on the development of VEGF Trap-Eye, Regeneron was the primary sponsor of the DA VINCI trial and interfaced with the clinical investigators on its execution. *See* Ex.1031, 8; Ex.2016, 7.

A. My and other clinical investigators’ roles in the DA VINCI trial

36. I was a clinical investigator on the DA VINCI trial. My role, like that of the other DA VINCI clinical investigators, was to execute the clinical trial protocol at my clinical trial site. Specifically, the other clinical investigators and I were responsible for recruiting subjects, obtaining their informed consent, administering the study drug and laser treatment to those subjects in accordance with the clinical trial protocol, reporting adverse events, and documenting the information

¹² CDER Approved Labeling for BLA Application 125156 (Lucentis®) (2006).

required by the clinical trial protocol. We also received monitors who visited to site to ensure adherence to the protocol and collect our data to report back to Regeneron. Some of these tasks were performed by the clinical investigators, and others were performed by staff under our supervision. DA VINCI was a double-masked trial, so each site had both masked and unmasked clinical investigators. Unmasked investigators administered the study drug and laser treatment, whereas masked investigators assessed adverse events and efficacy.

37. I did not play a role in developing the DA VINCI clinical trial protocol. Neither I nor, to my knowledge, the other clinical investigators chose to test VEGF Trap-Eye in DME, chose the dosing regimen for the VEGF Trap-Eye arms, or chose the visual acuity endpoints. My understanding was that Regeneron, as the study sponsor, had the idea to include these features before communicating them to the clinical investigators, and Regeneron made the final decision to proceed with this clinical trial with these features. This was consistent with the usual role of study sponsors in industry-sponsored trials.

38. Other clinical investigators and I authored publications describing the results of the DA VINCI trial. *E.g.*, Ex.2014, 1. The usual practice in the field, which was followed for DA VINCI, was to include some of a trial's clinical investigators as authors on publications of the results. For example, clinical investigators who played the largest roles in executing the clinical trial protocol and

preparing the article for publication were typically named as authors. The fact that a clinical investigator is listed as an author on these publications does not imply that they chose the disease, dosing regimen, or endpoints of the trial.

B. My and Dr. James Major's roles on the 2010 ARVO Abstract

39. Following the last 24-week study visit, Regeneron reported the top-line results in a press release on February 18, 2010. Ex.2020.

40. Around the same time, Regeneron sought to have the 24-week results presented at the 2010 Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in Fort Lauderdale, Florida, scheduled for May 2-6, 2010. It was the usual practice of Regeneron and other pharmaceutical companies to choose one of the clinical investigators to present clinical trial results.

41. By the time the 24-week DA VINCI results became available, the deadline to submit abstracts for the 2010 ARVO Annual Meeting had passed. However, ARVO made an exception for "late breaking" abstracts reporting research and data not available by the first deadline.

42. On February 25, 2010, Regeneron contacted me about submitting the 24-week DA VINCI results to ARVO. Ex.2077, 2. I received an email from Dr. Alyson Berliner, a Regeneron employee who was involved in the execution of the DA VINCI trial. *Id.* She asked if I would be willing to submit the 24-week DA VINCI results to ARVO as a late-breaking abstract. *Id.* I agreed, and on February 26,

Dr. Berliner sent me a draft abstract to review. Ex.2077, 1. She re-attached this draft to a follow-up email on March 1, 2010. Exhibit 2077 is a true and correct copy of Dr. Berliner's email sent to me on March 1, 2010, and Exhibit 2022 is a true and correct copy of the draft abstract attached to Dr. Berliner's email.

43. The draft abstract that Dr. Berliner provided me stated that that DA VINCI was a trial assessing VEGF Trap-Eye in patients with DME, described the VEGF Trap-Eye dosing regimens tested, and stated the top-line visual acuity results at 24 weeks. It was typical industry practice for the study sponsor to provide a full draft abstract with this information, as Dr. Berliner did, rather than ask a clinical investigator to prepare the first draft. And consistent with industry practice, when the abstract was submitted, I only had access to the top-line results provided in the draft abstract and Regeneron's public press release, Ex.2020. I did not have access to the full results used to calculate the averages reported in the abstract.

44. I did not make any material changes to these portions of the abstract. Dr. Berliner and I exchanged revisions of the abstract on March 2 and March 3. Exhibits 2023 and 2078 are true and correct copies of emails exchanged between Dr. Berliner and myself regarding these revisions, and Exhibit 2079 is a true and correct copy of the revised draft abstract that I sent to Dr. Berliner on March 2. Exhibit 2080 is a true and correct copy of the attachment to my March 3 email to Dr. Berliner, Exhibit 2023, and it is a copy of the version of the abstract I

submitted to ARVO on that date. Through these revisions, the language quoted in the table below stayed the same, which can be seen by comparing Exhibit 2022 with Exhibit 1010:

Feb. 26 Draft Abstract (Ex.2022)	2010 ARVO Abstract (Ex.1010)
DA VINCI: DME And VEGF Trap-Eye: INvestigation of Clinical Impact: Phase 2 study in patients with Diabetic Macular Edema (DME) ... DA VINCI is ... designed to assess safety and efficacy of 4 dose/dose intervals of VEGF Trap-Eye (VTE) ...: 0.5mg q4wks, 2mg q4wks, 2mg q8wks, 2mg prn At 6 months, the mean change in BCVA for each VTE group ranged from +8.5 to +11.4 letters ..., and no significant difference was noted among the VTE arms.	DA VINCI: DME And VEGF Trap-Eye: INvestigation of Clinical Impact: Phase 2 study in patients with Diabetic Macular Edema (DME) ... DA VINCI is ... designed to assess safety and efficacy of 4 dose/dose intervals of VTE ...: 0.5mg q4wks, 2mg q4wks, 2mg q8wks, 2mg prn At 6 months, the mean change in BCVA for each VTE arm ranged from +8.5 to +11.4 letters No significant difference was noted among the VTE arms.

45. ARVO had a policy that late-breaking abstracts could be submitted only by a first author who had not already submitted an abstract for the annual meeting. *See* Ex.2077, 1. Under that policy, I was ineligible to be the first author on

the abstract. I recommended Dr. James C. Major, my colleague, and another investigator on the DA VINCI trial, to be named as the first author. For this reason, I added Dr. Major's name to the abstract in the draft I sent to Dr. Berliner on March 2. Ex.2079.

46. The final version of the abstract also lists as an author the "DA VINCI Study Group." Ex.1010. The DA VINCI study group includes the set of clinical investigators on the DA VINCI trial, whose role in the trial I have described in ¶ 37 above.

47. Neither Dr. Major nor I are the source of the dosing regimen or the clinical trial results described in the 2010 ARVO abstract and quoted in the above chart. I consider that information to be the work of Regeneron as the study sponsor, and not of any clinical investigator. Dr. Major and I were responsible for executing these aspects of the clinical trial protocol at our site and presenting the data provided by Regeneron.

* * *

IPR2023-00884

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: February 21, 2024

A handwritten signature in black ink, appearing to read "David M. Brown", written over a horizontal line.

David M. Brown, M.D.